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CONTENTS

	PAGE
Physiological, Chemical and Clinical Studies on Pituitary Principles. By Dr. John J. Abel	305
Rheumatic Lesions of the Left Auricle of the Heart. By W. G. MacCallum	329
The Protective Power of Normal Human Serum Against Pneumococcus Infection. By Paul W. Clough	330
The Treatment of Post-Encephalitic Parkinson Syndrome with Hyoscin Hydrobromide, with a Note on the Mental Attitude in this Syndrome and a Report of 18 Cases. By Leslie B. Hohman, M. D.	335
Books Received	339
Notes on New Books	341
A Correction	344

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PHYSIOLOGICAL, CHEMICAL AND CLINICAL STUDIES ON PITUITARY PRINCIPLES*

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The designation *Hypophysis cerebri* for the organ concerning which I am to address you this evening is to be preferred to the more ancient one, *Glandula pituitaria cerebri*, for the reason that the former conveys no idea other than that of location in reference to the cerebrum, while the qualifying adjective, *pituitaria*, of the second designation connotes a secretory function and definitely commits one to a theory of external secretion of the organ. The word *pituita*, as used by Cicero and other writers of the classical period of Roman literature, means mucus, slime or phlegm, and our predecessors of an earlier day from Galen to Vesalius developed the theory that the brain voids mucus and excrementitious matter through the infundibular stalk into the body of the gland whence these filter down in some way into the nose and upper pharynx. The term *colatorium*, or strainer, was frequently applied to the gland and we are told by Hyrtl that the word *scutina* was also used in this connection. Now this latter term, like *pituita*, was in good use in the classical period and was applied to the filthy water that collects at the bottom of a ship—the bilge-water, and was furthermore used to designate the lowest of the people, the dregs, refuse or rabble of a city or state. I have ventured to call your attention to these words and their meaning because it is plain that the writers of Galen's day (131-200 A. D.) had committed themselves to this definite theory of the function of the hypophysis. To them it was very obviously an organ of external secretion with whose help the brain got rid of excrementitious matter much as the liver secretes bile into the digestive tract. I have not made any extended historical study of earlier writings on this subject and cannot state how long this theory that the hypophysis is a detergent organ of the brain persisted. Cushing has called attention to the fact that Richard Lower published a dissertation in 1672 (*Dissertatio de Origine Catarrhi*) in which he seems to have been the first to disprove the Galenic theory of pituitary function. "For whatever serum is separated into the ventricles of the brain and issues out of them through the Infundibulum of the *Glandula pituitaria* distills not upon the palate but is poured again into the blood and mixed with it." It must, however, have been believed in until

*The Harvey Lecture delivered in New York, April 12, 1924.

close to the middle of the 18th Century, if not later. Only the other day I came upon the theory in looking up a point in the excellent treatise of Nicholas Monardes, a small book in which that very judicial-minded Spanish physician describes the remarkable new drugs that had been brought to Europe after the discovery of the new world, their physical properties, mode of administration and especially their therapeutic or curative powers. Monardes is writing a little later than the middle of the 16th Century, at the close of the life-time of Andreas Vesalius. The first edition of his book appeared in 1565, a second in 1569 and a third in 1571. The second edition was translated in 1569 by the distinguished botanist, C. Clusius, into Latin, and there it is stated that one of the many remarkable attributes of a pill made by chewing tobacco leaves with burnt lime from mussel shells is to conduct away the slimy juices of the brain which, passing into the stomach, are later digested! There is no specific mention of the hypophysis in this statement of Monardes, as he evidently assumes that his reader is familiar with the mechanism by which slimy juices pass from the brain into the stomach.

I have descanted for a few moments on these ancient terms, *pituita, colatorium* and *sentina* and the definite theory of external secretion which originated their employment, because it may be safely asserted, I think, that a century hence, when our successors read the literature of our day in respect to the endocrine organs, they will have fully as much ground for amusement or for criticism as we have when we read that the function of the pituitary gland in the human being is that of affording an outlet for the slimy juice of the brain. When it comes to some of the lower animals, as the myxinoid fishes in which the pituitary tube opens on the roof of the head, where its external opening serves as an external nostril for the olfactory organ, the idea of a slime-excreting organ may not be so fanciful after all. Also bear in mind that we possess a pharyngeal hypophysis (5 mm. long) which is regarded as an actively functioning gland, and that there exists a canalis cranio-pharyngeus which is generally closed but in which, though very rarely, the entire hypophysis may be lodged. According to Gaskell's theory, indeed, the infundibulum or stalk of the posterior part of the pituitary body represents an ancestral mouth to which the ventricles of the brain and the central canal of the cord acted as the stomach and intestine. To cite his own words, "I have described how my investigations into the Vertebrate nervous system have led me to the conclusion that that system is composed of nervous material grouped around a central tube which was originally the alimentary canal of the Invertebrate from which the Vertebrate arose..... I have purposely omitted the consideration of the pituitary body because it does not in reality belong to the central nervous system, it represents, in my opinion, the Crustacean green glands, and will be considered when I come to deal with the formation of the Vertebrate skeletal tissues, and of the excretory organs."

Bremer, a recent Belgian reviewer of our present knowledge of the physiology of the hypophysis, prefaces his article with this statement: "The significance of the hypophysis remains a mystery, but hypotheses and theories abound and there is a singular contrast between the abundance and assurance of the current theories in respect to the functions of the gland and the rarity and incertitude of established facts." Percival Bailey who wrote an admirable paper entitled "Die Function der Hypophysis cerebri" in *Ergebnisse der Physiologie* for 1922, but who could not take into account any work published later than December 1921, also comments on the unsatisfactory character of the experimental basis of the theories which are now being exploited by certain overenthusiastic clinicians.

One is almost tempted to say of the hypophysis what Fontani said of the brain more than one hundred and ninety years ago: "Obscure as to its texture (structure), more obscure as to its diseases and most obscure of all as to its functions" ("obscura textura, obscuriores morbi, functiones obscurissimae"). The state of affairs is after all not quite so bad as this; I would not have you look upon me as a pessimist in this field, as one who is inclined to belittle our knowledge in respect to the organs of internal secretion, quite the contrary. May I not digress for a moment, in order to clear myself of the possible charge of underrating the importance of endocrinology? One has only to turn back to the textbooks and medical encyclopedias of 40 years ago to realize the extraordinary importance of the great number of actual facts at our disposal today. The very notable discovery of Addison in 1849 in respect to the constitutional and local effects of disease of the suprarenal capsules and the significant biochemical observation of Vulpian in 1856 that the fluid expressed from the interior of these capsules turns green on the addition of ferric chloride, like the still earlier very remarkable experimental physiological work of Berthold in 1849, which last proved conclusively that the testes (and the ovaries by inference) have an internal secretion which is responsible for the secondary sex characteristics, did not at once arouse investigators to take up work in endocrinology, all along the line, as one looking back on that period would have thought to be the case. Even the great discoveries of Claude Bernard (1857) in reference to glycogen and his definite assertion that the liver is to be regarded as an organ of internal secretion (although this phrase, according to Gley, was first used by Charles Robin in the sixties and by Paul Bert a little later) because it stores carbohydrates in the form of glycogen and at need converts this into blood sugar which passes into the blood stream, did not cause that rush into the endocrine gold fields which started in the later '80s of the last century. This stampede may be said to have been

due to a number of discoveries all of which took place within a few years of each other and during my own apprenticeship as a researcher. It is an established fact that the earliest discoveries of Addison in 1849, of Vulpian in 1856, of Bernard in 1857, of Berthold in 1849, of Basedow in 1840 and of Graves in 1835, of Brown-Séquard in 1856 and of Schiff in 1859-1866 did not either individually or collectively by their own importance, great as this was in each instance, start that attack on these problems of endocrinology on a wide front which is so marked a feature of present-day science. More was required and one of the most stimulating of the newer discoveries was that of replacement therapy. The events I refer to are the following: (1) Marie's announcement in 1886 of his discovery of a "peculiar non-congenital hypertrophy of the upper, lower and cephalic extremities," a condition now known as acromegaly, and the suggestion which was thrown out a year later (1887) by Minkowski that the hypophysis plays a rôle in this syndrome. (2) The discovery of Sandström (1880) that in human beings and mammals certain hempseed-sized glands are situated in or in close proximity to the thyroid glands, and the experimental demonstration of Gley in 1890-1891 that these apparently insignificant structures stand in a peculiar and causal relationship to tetany. (3) The theory of Moebius, announced by him in 1887, that Graves' or Basedow's disease is due to an abnormally increased activity—a hyperfunctioning of the thyroid gland. (4) The demonstration of Murray in 1891 that the myxedema, described by Gull in 1872 and studied by Ord (1878), Hadden (1882) and others, could be greatly alleviated or even cured by the administration of thyroid extract. Swiss surgeons, the two Reverdins and Kocher, had previously found (1882-3) that total thyroidectomy is followed by a post-operative condition very similar to this spontaneous myxedema of the English physicians. (5) The demonstration in 1889 by von Mering and Minkowski that complete removal of the pancreas from dogs was followed by a state of disease which resembled in practically all respects severe diabetes mellitus in man. That very notable discovery was immediately followed by experimental work in the same field by Hédon (1892), by Lépine and others, and was the forerunner of all those extraordinary discoveries in regard to the pancreas that have now culminated in the preparation and practical use of insulin by Banting, Best and Macleod and their collaborators. (6) Brown-Séquard's positive statement in 1889 that the subcutaneous injection of testicular extracts into human beings exercises a marked tonic influence, more particularly in elderly individuals, as was claimed by him to have been demonstrated in his own case, must also be recalled here. For while this work of Brown-Séquard was far from convincing, it nevertheless excited universal attention. In the opinion of his compatriot Gley "it has proved to be of epoch-making significance."

It will be seen that the six significant events which I have here enumerated all fall within the years 1887 to 1891, *at least it may be stated that the particular part of each of these events which is most significant in regard to its effect on the study of the endocrine organs falls in this short space of four years.* It was only in the later eighties, as many of us can testify who walked the wards at that time, that the more advanced of our clinical instructors began to call the attention of their students to some of the new marvels. I can recall as if it were yesterday the first case of myxedema which I had the opportunity to study when I was a graduate student of medicine in Nothnagel's clinic in Vienna in the autumn and winter of 1888-9. Little, I think, did some of our teachers of that day foresee that these examples of disease which were regarded more or less as interesting rarities were to open up a new world to investigators in the biological and medical sciences.

Immediately, in the early nineties, chemists and physiologists and pathologists all began to be very active in this field and endocrinology began that advance which has continued to this day and will no doubt continue to hold the attention of students for centuries to come. The thyroid and suprarenal glands were successfully attacked on the chemical side in the nineties. Physiologists, as Schafer and Oliver, Cybulski, Howell, Szymonowicz and many others, found that extracts of various endocrine glands, as the adrenals and the hypophysis, intravenously administered, exerted the most surprising effects on the cardiovascular and other structures of the body. And how extraordinary has been the course of discovery since the early nineties of the last century! Secretin, Insulin, Thyroxin, Epinephrine, Pituitrin and other names of endocrine principles come to mind as indicating the progress that has been made possible by the conjoint labor of clinicians, physiologists, pharmacologists, chemists, pathologists and biologists. We now speak with confidence and familiarity of hormones, growth principles, vitamins and the like, substances which in very minute amounts act as chemical or humoral integrating agents, or as stimulating or sensitizing agents for particular structures of the body. We speak of the interactions and interdependence of many of the endocrine organs, although we are here dealing with most intricate and involved mechanisms. New evidence is, however, coming to hand almost daily in support of the thesis that an interrelationship exists between some at least of the most important of the endocrine organs. Much of this new evidence is being furnished by the younger school of experimental zoologists here and abroad.

It may be questioned if there is a single branch of the medical art that has remained uninfluenced by the discovery of the functions of endocrine organs. Only the other day my colleague Professor Meyer was commenting to me on the enormous significance of the abnormalities

of one or more of the structures as affecting the behavior response of his patients toward their environment. At the time of our conversation an autopsy had been made upon a young woman, a homo-sexual pervert, who had committed suicide. The sexual organs, particularly the uterus, were very poorly developed and the suprarenal glands were among the smallest ever encountered in our autopsy rooms. The influence of the endocrine organs, more especially the gonads, on the psychic response of an individual to his environment appears to be generally admitted. Their influence on our physical make up is also beyond question. The thyroid gland is especially important among these organs because of its extraordinary influence in intra-uterine life on both mind and body. Taking the two things together, that is to say, the influence of endocrine organs on both mental and somatic processes, it is not surprising that many see in the action and interaction of these organs, in their greater or lesser activity, in their influence on heredity, and in the assumed relations that subsist between some of them and the autonomic (sympathetic plus parasympathetic) nervous system, a full explanation for the differences in mind and body that exist between any two individuals taken at random from among the millions of any given race.

(At this point the lecturer showed two models of a recently removed human hypophysis, which were exact reproductions of both the size and natural appearance of the two main divisions of the gland. He also showed similar replicas of the bovine hypophysis, calling attention to the fact that the human gland weighs on the average only 0.612 gram (Erdheim), while the bovine gland weighs about 2.4 grams (Houssay), and that in both instances the neural or posterior lobe, with whose chemical composition and functional character this lecture is mainly concerned, constitutes only about one-sixth of the active hypophysis. Drawings were also exhibited in which the lesser divisions of the organ, the pars intermedia, pars tuberalis and infundibular stalk, were shown. The histological differences in the structure of the various divisions were briefly described. Since it was necessary to discuss certain recent findings of the lecturer in respect to the pharmacological properties of the tissues composing the floor of the third ventricle, anatomical drawings of the hypothalamus and the contiguous parts of the brain were shown and a brief account of our fragmentary knowledge of the physiological significance of this region of the brain was given.)

What are the chemical principles that have to be considered in the case of the hypophysis? Robertson has given the name tethelin to the growth principle of the anterior lobe and he has separated from this lobe a mixture of substances which he believes to contain this principle. This mixture, it is stated, produces striking effects on the metabolism and growth of experimental animals, but it must be borne in mind that thus far no chemical individual, whether it be given the name of tethelin or any other, has yet been isolated from this lobe, as is frankly admitted by Robertson. P. E. Smith of the University of California finds that Robertson's alcohol soluble tethelin does not favor the growth of hypophysectomized tadpoles. Smith could get such tadpoles to grow only after feeding them the insoluble residues from which the tethelin had been removed by Robertson's methods. Robertson declares that the negative results which Smith has obtained by feeding hypophysectomized tadpoles with tethelin is due to the fact that he has added this principle in the form of a solution to the water in which the tadpoles exist and that the animals do not absorb the principle in sufficient concentration to get its physiological effect. It is evident, therefore, that we are encountering absolutely contradictory statements in reference to the physical and chemical properties of the growth principle which is undoubtedly present in the anterior lobe of the hypophysis in amphibia. And whether it is mainly found among the alcohol soluble principles of the gland or remains in the less soluble residue appears for the time being to be undecided.

That a growth-maintaining principle of an unknown chemical nature is present in the anterior lobe of the hypophysis of amphibians has, however, been established with certainty. In addition to that of Smith, the work of Allen with tadpoles of *Rana pipiens*, that of Uhlenhuth with *Amblystoma* larvae, and that of Huxley and Hogben with the Mexican salamander, *Amblystoma tigrinum*, have yielded results of the greatest value in this field.

Evans and his collaborators have recently demonstrated that characteristic effects upon growth, oestrum and ovulation can be induced in rats by the daily *intraperitoneal* injection of fresh anterior lobe substance. We have here further evidence of the existence of a specific hormone (or hormones) in the hypophysis. A further consideration of this newer work must be left to Professor Evans who is to follow me in a lecture in which he will no doubt give a full account of his own experiments with anterior lobe extracts as well as of those of his predecessors.

The much smaller posterior lobe has been worked at very intensively during the past twelve years or more, and we are now getting much definite information in respect to its active principle. Physicians employ a simple extract which is furnished in the form of a sparkling clear solution in small sealed ampules that contain 0.5 or 1 c.c. This simple watery extract which contains all of the chemical substances present in the gland, except the proteins and certain lipoidal constituents, is of very great service in medicine, and especially in obstetrics where it rivals and often excels that old time remedy, ergot. Unfortunately, this highly active pituitary extract is often wrongfully used and has a number of times caused the death of women when used by inexperienced physicians or midwives. If employed in overdose and at the wrong stage of labor, its action on the uterus may be so violent as to cause this organ to be ruptured. There are many other both medical and surgical uses of this very potent drug. It has been found in recent years that it is the

only known substance that will quickly control the excessive flow of urine in that distressing condition known as diabetes insipidus. As is well known to all of you, in diabetes insipidus the patient may void 20 or more liters of urine a day and is tormented by an excessive thirst. Naturally it is very difficult for such persons to go about in society and to attend to their business. But now if a little of a good pituitary extract should be injected under the skin of such patients, or if it should be dropped into the nostrils, the excessive flow of urine will be promptly diminished, the thirst will disappear and the individual will soon be made quite comfortable. The daily urinary output will go down to a very few liters or may reach the normal. The remedy may have to be given every 3 or 4 hours at first and later perhaps but once a day. The remedy may be continued as long as the disease persists. This drug removes the symptoms in almost all cases of diabetes insipidus and is therefore of the greatest service to those afflicted by this disease.

Now what chemical principles are we dealing with in an extract of the posterior lobe? Is there more than the one hormone present? The early efforts of Cyon, Houssay and Engeland and Kutscher at isolating an active substance or substances from the hypophysis are of historical interest only. An abstract of the work of these investigators is given by H. Fühner in the historical introduction to his paper (1913) entitled "Pharmacological Investigations on the Active Principles of the Hypophysis." Until very recently the idea that this lobe contains three or four or even more specific principles has been firmly maintained by several investigators. Eleven years ago the skilled chemists of the Farbwerke-Hoechst Company (see Fühner) announced that there are four crystalline principles present. These chemists claimed to have isolated these principles in the form of sulphates. Later, not on the basis of chemical isolation but on conclusions which were drawn from the use of certain solvents and from physiological reactions, Dale and Dudley assumed that there are three characteristic principles and possibly a fourth. My collaborators and I have found ourselves unable to agree with the views of the above named investigators. Our position may be briefly put as follows, and we believe that our experiments demonstrate the correctness of our conviction. We hold that the bovine posterior lobe (including the pars intermedia and the neural portion of the hypophyseal stalk) contains only one specific principle, or hormone. This principle has been isolated by us in the form of a tartrate for which we can not as yet claim chemical purity and individuality, but which is of extraordinary potency as a smooth muscle stimulant, being 1000 to 1250 times more powerful than the acid phosphate of histamine, a base which has hitherto held the ranking position in this respect. Continued studies on our part have shown that this tartrate displays all of the characteristic physiological properties of a good aqueous extract of the posterior lobe of the hypophysis. In addition to its action on the uterus, it causes a prolonged rise in the arterial pressure, with constriction of the peripheral arterioles and capillaries, a brief diuresis in the green-fed rabbit, has an antidiuretic action in diabetes insipidus and affects the respiration of dogs and rabbits in a characteristic manner. A pituitary extract that has been prepared in such a way as to be quite free from blood pressure-lowering and broncho-constricting substances no longer affects the bronchi—unless it be in the way of causing a slight dilatation when given in great excess. Similarly, the tartrate of the specific principle of the posterior lobe fails to cause the slightest constriction of the bronchi and in very large doses causes a slight dilatation.

We have so far failed to find a single activity of a posterior lobe extract referable to a specific principle or principles which is not duplicated by our tartrate and we therefore conclude that the oxytocic, pressor, respiratory, diuretic-antidiuretic actions of our tartrate are but manifold actions of one and the same active principle or hormone.

Further evidence in favor of this belief is seen in the following facts: (a) All of the physiological properties of our active substance increase in intensity and in the same ratio *pari passu* with the methods of purification, from the initial precipitation of the fresh posterior lobe substance to the final precipitation of the tartrate. It is unlikely that all of these physiological properties would retain their relative position to each other throughout a long series of varied chemical processes were they not characteristic of one and the same principle. (b) Exposure of the tartrate to normal sodium hydroxide for one hour at room temperature *completely destroys all* of its physiological action. It is extremely unlikely that so comparatively mild a treatment as this should simultaneously destroy three or four separate principles. (c) Boiling a solution of the tartrate with 1 per cent hydrochloric acid under a reflux condenser for one half hour is also destructive of all of these physiological properties, with the exception of the oxytocic action, a certain proportion of which appears to withstand this short treatment with acid.

A communication has just been received from the pharmacological laboratory of Professor G. Modrakowski of Warsaw which supports my contention that the posterior lobe contains only one specific hormone. Doctors Leyko and Sikorski of that Institute have studied the blood pressure raising power of post-pituitary extracts on dogs at intervals of two days, the operation being performed under local anesthesia. The action of the extracts upon the urinary secretion of dogs with a permanent bladder fistula was then studied and it was found, as in their

previous experiments (1921), that the extracts promptly check the diuresis induced by the copious administration of water to the animals. The pressor and antidiuretic action of the extracts were then compared with their oxytocic action on the guinea pig's uterus and it was found that "these three actions go together." To cite a passage from the concluding section of their paper: "An extract giving a strong pressor effect acts with about equal strength upon the diuresis and vice versa. This seems to speak in favor of Abel's view that the extract contains only one main active principle acting in all three directions, and against the presence of a number of different active bodies in the gland, each acting only in one way."

Smith and McClosky in a paper soon to be published in the *Journal of Pharmacology and Experimental Therapeutics* and from which I have the privilege of quoting, have also made a valuable contribution to the point under discussion. These investigators "have studied the diffusion rate of the several physiologically active constituents of the infundibulum through a series of collodion membranes of graded permeability," and conclude that "the identical diffusion rate of the oxytocic, pressor and renal activities present in infundibular extracts argues in favor of their chemical identity, and confirms the view held by Abel and his collaborators on this matter."

But while the posterior lobe and pars intermedia contain but one specific principle possessing these manifold physiological properties, it must be borne in mind that it also contains in small amounts two depressor substances which cannot be said to be characteristic of this part of the hypophysis, although both are found in larger amount in the posterior than in the anterior lobe. These two blood pressure lowering substances have been named the "B" and "C" substances in an earlier paper (Abel and Nagayama) in which also the specific principle of the posterior lobe which has now been separated in the form of a highly active tartrate was named "A." The two depressor substances, "B" and "C," are completely separated from the pressor-oxytocic-diuretic-antidiuretic substance "A" by our chemical methods, as will be shown presently. "C" is histamine. This base was first isolated in the form of a pure picrate from the dried whole pituitary by Abel and Kubota in 1919. At that time I supposed that this base represented the entire oxytocic value of the posterior lobe, taking for granted in those days that this lobe contains several active principles. My own further studies in this field, as also the communications of Jackson and Mills and of Dudley showed me that I had exaggerated the rôle of histamine in pituitary extracts. I at once admitted the correctness of the position assumed by these writers, that the real uterine stimulant, the "A" substance, above referred to, and histamine are two distinct chemical individuals. It was then intimated by some writers (Hanke and Koessler) that the histamine which Kubota and I had isolated from the hypophysis was probably of bacterial origin. This suggestion has been proved by Roca in my laboratory to be entirely unfounded. Roca has demonstrated that histamine or the "C" substance is obtainable by mild treatment with acids from the hypophysis when the glands are gathered at the slaughter-house and are either immediately placed in boiling water or sliced into corrosive sublimate solution as they are taken from the skulls of the beeves. Histamine is not present in the free form or as a simple salt in the entirely fresh gland, but it always appears when the ground-up hypophysis is boiled with acids in the usual process of deproteinization of the extracts. It is also present, in a small amount to be sure, in our commercial extracts, as has been shown by Jackson and Mills and in my own laboratory. This agent together with the "B" substance is responsible for the broncho-constrictor and perhaps other actions which are not given by the purified hormone, or "A" substance. All of the earlier commercial extracts, which were often boiled for too long a time and in the presence of too much acid, always contained more depressor material than do the commercial extracts of the present day. Roca has shown that, after destruction of the "A" substance by acid, a posterior lobe extract will be 7 to 8 times more depressant for the arterial pressure than is a similarly treated extract of the anterior lobe and that chloroform takes up from the posterior lobe material thus treated about 20 times more histamine than is obtainable from the anterior lobe similarly treated. Abel and Kubota have shown that the precursor of histamine from which histamine is easily liberated by acid hydrolysis and which cannot be histidine, is widely distributed in the body, being present in the liver, the gastric mucosa and elsewhere.

A second depressor substance, "B," has been described by Abel and Nagayama. It differs from histamine in being entirely insoluble in chloroform and also in other respects. It has not as yet been prepared in any form other than as an amorphous water-soluble residue, soluble in 90 per cent alcohol and which has the properties of an albumose. It gives the biuret reaction and can be salted out with ammonium sulphate or with sodium chloride. It corresponds in its physical and physiological properties with a similar chloroform insoluble depressant material that can be separated from tissue extracts in general. It is therefore a widely distributed principle and it is to be regretted that no extensive attempts toward its purification and isolation have been made.

To recapitulate my position: Extracts of the pars intermedia and the posterior lobe of the bovine hypophysis contain only one specific hormone, the "A" substance of Abel and Nagayama which has been isolated in the form of a more or less pure tartrate and which exhibits all of the manifold characteristic physiological actions of the posterior lobe. My position is diametrically opposite to that of certain other investigators (Führer, Dale and

Dudley) who assume that at least three and even four or more (Führer) specific hormone principles exist in the extracts of the posterior lobe.

In a properly made extract of the posterior lobe this powerful "A" substance entirely overbalances the action of the two other substances which are always present to a small extent, the amount being greater when an extract has been exposed to the action of weak acid and heat for too long a time. The earlier literature on this subject contains numerous blood pressure tracings whose character shows at a glance that the authors in question were working with damaged extracts. It is seen in such tracings that the pressor effect does not immediately follow upon the injection of the pituitary extract, as should be the case, but is preceded by a fall in the blood pressure which is often very pronounced, and it is only after this depressor action has worn off that the belated pressor effect is observed. It is only such damaged pituitary extracts that induce in the dog a pronounced broncho-constrictor action.

One of the two minor substances, "C," is histamine which exists in the hypophysis as in many other locations in the body in the form of a labile precursor of unknown properties and composition. The other or "B" substance, also a blood pressure lowering and mildly oxytocic agent, differs from histamine in being entirely insoluble in chloroform, giving the biuret reaction and having the properties of a proteose, as at present isolated. I would, however, not be understood as saying that the substance is in reality a proteose. It may be a substance of simple composition which is merely admixed with or adsorbed on proteoses.

Outline of Method of Isolation

Preparation of the mercuric chloride-protein cake. The whole bovine glands are placed in cold storage at the slaughter-house immediately after their removal from the skulls of the animals; the following morning the posterior lobes are trimmed out and ground to a very fine paste and each 100 grams of this paste is thoroughly mixed with 100 c.c. of 0.35 per cent hydrochloric acid containing 4 grams of mercuric chloride, and placed in a tightly stoppered bottle of such a size that the air space above the contents is as small as possible. When the mixture is received at the laboratory, it is treated with 10 grams of solid mercuric chloride, shaken several hours and filtered by suction. The insoluble "cake" is washed twice by grinding with about 25 c.c. of saturated mercuric chloride solution and filtered by suction. During the past winter we have found it advisable to depart somewhat from the above procedure. The glands are chilled as before, but the separated posterior lobes (plus pars intermedia) are defatted with acetone after being first ground to a fine paste. The defatted material reaches us in the form of a white powder which is ground up with solid mercuric chloride and 0.2 per cent hydrochloric acid solution. The mixture is then shaken for several hours in a shaking machine and the cake is washed twice by grinding with saturated mercuric chloride solution and filtering by suction.

The pars intermedia of the hypophysis of the ox closely invests the posterior or neural lobe and cannot readily be separated from it. In our work it was naturally always utilized along with the neural lobe. Unless otherwise stated, all so-called bovine posterior lobe extracts are in reality extracts of these two divisions of the hypophysis, both of which contain the active principle under discussion. That the pars intermedia substance can be obtained in the pure condition and that extracts made from it have a pressor and other physiological actions has been amply proved by Herring, Lewis, Miller and Mathews, Biedl, Houssay, Atwell and Marinus and others. Osborne and Vincent concluded from their experiments that an extract made from the central part of the posterior lobe—devoid of epithelial elements—is much more active in raising the blood pressure than one made from the peripheral epithelial part, and expressed the opinion that probably the external layer would be found to be inactive if it could be obtained quite free from admixture with the central portion. Schafer and Herring also found the central portion of the neuro-hypophysis to be more active as a diuretic than the external layer. In Vincent's exhaustive review on the functions of the hypophysis (1915) the work of Foderá and Pittau, of Salvioli and Carraro, and of Houssay and his pupils is cited in support of his conclusion "that it is the nervous portion proper of the organ which contains the substance or substances having such pronounced pharmacodynamical properties different from those possessed by other kinds of nervous tissue," and he further finds himself "strongly inclined to adopt the view of Houssay that the substance or substances are secreted by the cells of the pars intermedia, and then collected and concentrated or changed into more active forms in the nervous portion proper."

The investigations of Atwell and Marinus (1918) harmonize many of the differences that are found in the observations of their predecessors. These writers have also shown that the weak physiological effects given by extracts of the pars tuberalis are due to the inclusion of some of the neural stalk substance during the preparation of the extract. In other words pure extracts of the pars tuberalis are devoid of the pressor, oxytocic and other actions so characteristic of the posterior lobe extracts. They were also able to prepare pure extracts of the neural portion of the hypophyseal stalk which were found to have an action on the blood pressure of the dog and on the guinea pig's uterus in every way comparable to those obtained from a commercial pituitary extract. It may be accepted as proved that properly made extracts of the pars intermedia, of the neural portion of the hypophyseal stalk and of the posterior lobe itself are practically all of equal potency and exhibit all of the characteristic reactions of the posterior lobe extract.

An explanation of the contradictory findings of physiologists, not only in respect to the relative strength of the extracts of the several divisions of the hypophysis but also in respect to the location of the several postulated active principles, is now found in our fuller knowledge of the chemical properties of the real active principle. The ease, for example, with which this sensitive hormone can be altered in its properties by boiling at the wrong pH was unknown to our predecessors and this circumstance is

probably more accountable than any other for the confusion which has hitherto characterized the physiological as well as much of the chemical literature of the subject.

Liberation of the active principle from the "cake" and precipitation with phosphotungstic acid. The washed cake is ground with about 200 c.c. of water and the resulting suspension is neutralized to litmus paper with sodium hydroxide, treated with hydrogen sulphide in excess, then with about 40 c.c. of saturated sodium chloride solution (to flocculate the precipitate of mercuric sulphide) and filtered with the aid of very gentle suction. The filtration is quite slow and if too much suction is applied the paper easily becomes entirely clogged. The filtrate is aerated to remove the excess of hydrogen sulphide, treated with a 1:1 solution of phosphotungstic acid until precipitation is complete, and filtered by suction.

Decomposition of the phosphotungstate precipitate and precipitation with tannic acid. The precipitate is ground with ice-cold water and enough sodium carbonate solution to make the turbid solution barely alkaline to litmus paper and reprecipitated with hydrochloric acid, the solution in sodium carbonate and reprecipitation with hydrochloric acid being repeated twice more. Generally, the first treatment with sodium carbonate leaves undissolved a small amount of yellow residue which is usually filtered off, but no effort is made to obtain a clear filtrate. The reprecipitated phosphotungstate is finally taken up in dilute sodium carbonate solution and treated, ice-cold, with hot saturated barium hydroxide solution, drop by drop, until precipitation is complete, and filtered from the barium phosphotungstate. To the filtrate dilute sulphuric acid is added until no further precipitate is formed; together with the barium sulphate there is thrown down a small amount of a flocculent substance which apparently carries down some of the hormone by adsorption, for when the mixed precipitate is treated with dilute sodium carbonate solution and filtered, the filtrate always shows more or less oxytocic activity. The filtrate from the precipitate formed by the sulphuric acid is neutralized with sodium hydroxide and treated with a concentrated aqueous solution of tannic acid and then with solid powdered sodium chloride until the latter no longer dissolves, the mixture being thoroughly stirred throughout the addition of both the tannic acid and the salt. The precipitated tannate is filtered off and more tannic acid and salt are added to the filtrate; this produces a second precipitate, the filtrate from which is treated a third time with tannic acid and salt. The final filtrate is now usually found to be entirely devoid of any action on the uterus. The combined tannate precipitates are washed by grinding several times with saturated sodium chloride solution and filtering by suction, and are pressed as dry as possible on the funnel with a glass rod.

Conversion into the tartrate. The tannate precipitate, while still moist, is ground with a little 95 per cent alcohol and 1 or 2 c.c. of a saturated alcoholic solution of tartaric acid, and the resulting thick solution is pipetted off from the undissolved residue, which is again ground with a little alcoholic tartaric acid, the process being repeated until the residue, which consists largely of sodium chloride, is practically colorless. The alcoholic tartaric acid extracts are treated with much anhydrous ether (at least 20 volumes) and the resulting precipitate is again taken up in alcoholic tartaric acid and reprecipitated with ether, the process being repeated three times.

The tartrate is now collected on a hardened paper and immediately transferred to a vacuum desiccator charged with phosphorus pentoxide. It has been our experience during the past few years that our salts remain unaltered when dried in this way, while the tension of sulphur trioxide in desiccators charged with sulphuric acid appears to be great enough to injure our labile substance. This seems also to have been the experience of Burn and Dale.

Purification with picrolonic acid. The tartrate is ground with a little water and, without removal of the small amount of material which may remain undissolved, is treated, ice-cold, with a saturated solution of picrolonic acid in alcohol. The considerable precipitate thus obtained consists of foreign picrolonates and carries down with it only a small amount of the active material. The precipitate is removed by filtration and more of the alcoholic solution of picrolonic acid is added together with some cold water. An additional amount of the foreign inactive picrolonate is thus removed. This process is repeated as long as any considerable amount of picrolonates can be precipitated.

We have here a good instance of non-adsorption as compared with the earlier precipitates, which adsorb the hormone quantitatively. The clear supernatant fluid containing the active principle is shaken a few times with ether to remove the excess of picrolonic acid and is then poured into small shallow glass bowls in which it is allowed to evaporate in a current of air at room temperature. When the solution has become rather concentrated, it is again tested with picrolonic acid in alcohol, and if it again gives a considerable precipitate, the process of purification outlined above is repeated and the solution is allowed to evaporate to dryness. The air-dried residue is taken up in 93 per cent alcohol (which may profitably contain a small amount of tartaric acid) and precipitated with much ether. The precipitate is washed with alcohol-ether (1:20) and dried over phosphorus pentoxide. The tartrate thus obtained is highly active for the guinea pig's uterus. According to the care with which the above operations have been carried out and more especially when the injurious action of acids or other agents has been avoided, this tartrate will be found to be

from 125 to 250 times more powerful in its action on the uterus than the acid phosphate of histamine.

Nature of the precipitate obtained with picrolonic acid. The precipitated picrolonates appear to consist mainly, if not entirely, of biuret-yielding proteoses. These are recovered from the precipitate by the simple process of dissolving them in acidulated water (HCl), removing the freed picrolonic acid by repeatedly shaking with ether and allowing the aqueous fluid to go to dryness in a current of air at room temperature. The residue gives no signs of crystallizing, gives the biuret reaction with great intensity and is of low oxytocic value (only $3 \times \beta$-I phosphate). By repeatedly salting it out from its solution in water by the addition of powdered sodium chloride, the oxytocic titer of this substance may be still further lowered. This proteose-like body also gives a Pauly reaction and when warmed gently with hydrochloric acid gives a pink to plum color (Guggenheim's reaction). By the use of picrolonic acid a very considerable amount of this substance may be removed from the crude pituitary tartrate. Thus in a purification experiment recently made with this reagent, I started with 0.760 gram of a crude tartrate whose oxytocic titer was somewhat better than $50 \times \beta$-I phosphate. The picrolonates obtained from this weighed 0.2828 gram and the biuret-yielding substance recovered from this amount of picrolonates weighed 0.1170 gram which however did not represent the entire amount obtainable, as some of the material was used in making tests before it was weighed. When we take into account the small amount of active principle that adheres to the precipitated picrolonates and how large an amount of material is removable by this method, it will be seen that this step in our purification process is an advantageous one.

Further purification of the active tartrate. The further purification of the tartrate is effected by means of solvents and naturally, from this point on, is achieved only at the cost of the scattering of the active substance, since a sharp separation into entirely inactive and highly active fractions is impossible with the use of solvents alone. Nevertheless, it is possible, at this stage of the operations, to carry a tartrate with an activity of from 50 to 250 times that of histamine acid phosphate to a stage where it is 1000 to 1250 times as powerful as the histamine salt.

We hope to elaborate better methods for these final stages of the purification, that is to say, methods more nearly comparable to those involving the use of tannic or picrolonic acid rather than fractional precipitation with organic solvents. For that reason we give only a mere outline of our work with solvents as at present carried out by us.

Our active principle in the form of a "tartrate," if it may be described as such, as seems permissible from our procedure, is extremely soluble in 93 to 95 per cent alcohol, in water and in pyridine, much less soluble in absolute ethyl alcohol and in dry n-butyl alcohol, fairly soluble in methyl alcohol and quite insoluble in dry ether, chloroform, acetone and benzene. A very considerable increase in activity may be brought about by the expert use of absolute alcohol alone at room temperature. The judicious addition of n-butyl alcohol to a solution of the tartrate in 95 per cent alcohol throws out a fraction of less oxytocic activity, while a more highly active fraction remains dissolved in the mixed solvents and can be precipitated out with ether. The precipitate is then repeatedly extracted with absolute alcohol and the combined extracts are allowed to evaporate to a small volume in an air current at room temperature. This is the method which we have generally used to obtain our most highly active preparations. Pyridine also dissolves the tartrate, with its accompanying inactive impurities, with the greatest ease; from this solution a less active fraction can likewise be precipitated with n-butyl alcohol or absolute alcohol plus a trace of ether. In either case, after the filtrate from the relatively inactive precipitate has been concentrated to a small volume at room temperature, the highly active tartrate is precipitated with a large volume of ether and the precipitate is washed with absolute alcohol-ether (1:20) and quickly placed in a phosphorus pentoxide desiccator, so that no moisture condenses on it as the ether evaporates. In these ways 0.01 to 0.03 gram or more of dry white substance varying in oxytocic value from 600 to 1250 times histamine acid phosphate is obtained at a time. It may be noted here that this tartrate is now no longer separable by n-butyl alcohol into fractions which differ in their physiological action. Although the yield of the purest tartrate is not large, as we have just seen, that of the impure or first tartrate is generally quite satisfactory, considering the difficulties that are here encountered. For example, as much as 0.305 gram of the first or impure tartrate, with an oxytocic value of 50 to 75 times β-I phosphate, was recently obtained from 225 grams of fresh infundibular substance. In this instance no special measures were taken to insure a high oxytocic titer of this first product. Naturally, when the greatest precautions are taken and one or other step in the process is repeated, the first tartrate will generally have a much higher oxytocic value, but the yield will be less in quantity.

NATURE OF THE FINAL PRODUCT

We cannot yet claim that our final product, with its very high activity for plain muscle tissue and for the vascular and the renal apparatus, represents a single chemical individual. The repeated use of various solvents, as just outlined, appears, however, to have removed every trace of readily crystallizable material. When, for example, the tartrate which, we will say, has an oxytocic value of 250 times histamine acid phosphate, is dissolved in 93 per cent alcohol and the solution is allowed to evaporate, a considerable amount of substance separates

out in the form of beautiful, colorless, branching, fern-like crystals which give a positive Pauly but no biuret reaction. This material is devoid of physiological activity, at least as far as its action on the uterus, blood pressure and the kidney is concerned. The highly active remainder, on the other hand, when dissolved in 93 per cent alcohol or water and then allowed to evaporate, dries down to a colorless or nearly colorless amorphous layer.

The addition of 10 per cent sodium hydroxide solution to the tartrate (even the purest specimen) instantly liberates a gas which is alkaline to litmus and which smells strongly of an alkylamine mixed with ammonia. On adding a few drops of concentrated hydrochloric acid to a minute amount of the dry tartrate and warming gently over the free flame, a beautiful pink or violet color immediately appears. On standing, this color gradually changes to brown. We cannot be sure at this writing that the tartrate of highest purity will still give this test, as we have not applied it to preparations with an oxytocic value of more than 160 times β-I phosphate. This color reaction was first observed by Guggenheim when working with the pituitary extract known as "Pituglandol."

Neither picric nor picrolonic acid precipitates anything from an alcohol or aqueous solution of our final tartrate. Mercuric chloride and tannic acid (without sodium chloride) also fail to yield a precipitate. Phosphotungstic acid precipitates the active principle only very incompletely, even when the tartrate has the value of only 250 times histamine acid phosphate, a fact which leads us to suspect that this reagent will no longer precipitate the fully purified substance. The Pauly reaction is still given by our most highly active preparations, but as regards the biuret reaction our impression, at the moment of writing, is that it is not given with the same intensity as by less highly purified preparations and we must therefore reckon with the possibility that an albumose-like or peptide-like substance still contaminates our product unless indeed the active principle is itself a peptide-like substance.

In spite, therefore, of the extraordinary potency of our final product, we cannot be certain that we are dealing with a single chemical individual; on the contrary, we suspect that it still contains an admixture of some inactive constituent or constituents which are most likely proteose-like substances.

Comments on the Foregoing Method of Isolation

It is evident that the pars intermedia and the pars posterior of the pituitary gland cannot contain more than a very small amount of our active principle. A gram of fresh pars intermedia plus pars posterior substance contains, on an average, an amount of oxytocic principle equivalent to 0.25 gram of histamine acid phosphate, and since our purest specimen of the actual pituitary "hormone" is at least 1250 times more powerful than the histamine salt, it follows that one gram of infundibular tissue cannot contain more than 0.0002 gram (0.02 per cent) of this singular and potent substance. And it becomes evident at once that one cannot hope to isolate a principle present in such minute amounts from so complex a tissue as the pituitary infundibulum unless one can use methods by which it is possible to carry the principle along from step to step without material loss. The methods described above, when properly used, meet this requirement. They are based on the fact that the active principle is adsorbed by various flocculent precipitates which offer an enormous surface. But this procedure would have defeated our purpose had we not been able to discover methods for liberating the principle from the surfaces on which it is adsorbed.

The points involved in the use of mercuric chloride as a precipitating agent furnish illustrations of the principles here involved. When the finely minced infundibular substance is mixed intimately with an excess of acidulated mercuric chloride solution, the active principle is quantitatively adsorbed by the mercuric chloride-protein "cake." After disintegrating the cake and precipitating the mercury with hydrogen sulphide, the active principle can be liberated only by adding a sufficient excess of sodium chloride, which causes the colloidal mercuric sulphide to coagulate and so alters the surface conditions that the hormone is no longer adsorbed. In this connection it may be pointed out how greatly the various constituents of the neurohypophysis differ in their adsorbability by the mercuric chloride-protein cake, a difference which makes it possible to effect a clean-cut separation of substances that act on the blood pressure. From the cake itself we obtain only the pressor-oxytocic principle, while the filtrate from the cake yields all of the preformed depressor substances present in the ground up and acidulated infundibulum. Now mercuric chloride will not *reprecipitate* the principle from the solution obtained from the mercuric chloride-protein cake by the use of hydrogen sulphide and sodium chloride. Evidently, the large adsorbing surfaces of the precipitated proteins are necessary in order to bring down the hormone. However, a very simple expedient makes it possible to use a mercury salt as a precipitant a second time or as often as may be desired. It is only necessary to add first a sufficient quantity of disodium hydrogen phosphate to the solution of the hormone and then to add a solution of mercuric nitrate. The flocculent precipitate of mercuric phosphate evidently offers a suitable surface since, under the above conditions, the hormone is precipitated quantitatively. Here also, the free use of sodium chloride is necessary, in the precipitation of the mercury with hydrogen sulphide, in order to prevent adsorption. We have recovered as much as 90 per cent of a known quantity of our principle by this method of reprecipitation with mercuric nitrate.

Phosphotungstic acid also precipitates the principle quantitatively at the stage at which we employ this reagent. Later in our work, as concomitant inert substances were progressively removed, it was found that the phosphotungstic acid no longer precipitated the principle quantitatively and we therefore suspect that here, as in the case of the mercurials, the hormone is only adsorbed on the surface of (other) precipitated substances.

Tannic acid also acts in this way, i. e., it serves to furnish the necessary surfaces for adsorption as it falls out in flocculent form in the presence of sodium chloride. This acid yields no precipitate whatever when added to a solution of our purified tartrate which is free from electrolytes. The ready solubility of the precipitated tannates and of the excess of tannic acid in an alcoholic solution of tartaric acid and the relative insolubility of the tartrate of the hormone in an alcohol-ether medium makes it possible to remove the active principle from the tannic acid precipitate and obtain it in the form of a dry tartrate.

On the other hand, in picrolonic acid we have an agent which removes impurities from an aqueous solution of the hormone with only a trifling loss of the latter by adsorption. In this case the precipitated foreign picrolonates soon aggregate to yellow resinous lumps with no extensive adsorbing surface.

We hope that our methods of allowing our principle to attach itself to adsorbing surfaces from which it may again be liberated without serious loss will be capable of further improvement.

There is, of course, nothing novel in the ideas underlying the above methods. Other investigators in this and in other fields of chemical work have repeatedly noted that this or that active principle is often lost by what were thought to be instances of irreversible adsorption. It will be seen, however, that we have been fortunate enough to be able to turn to our advantage some of the instances of supposedly irreversible adsorption and to develop them into useful methods of isolation.

PHYSIOLOGICAL PROPERTIES OF THE PITUITARY TARTRATE

The following tracings give evidence of the various physiological actions—pressor, oxytocic and diuretic—of our substance. Figure 1 illustrates the action on the uterus of a product which, although crystalline, contained so much of the active principle admixed or adsorbed that its oxytocic value was 50 to 62.5 times that of histamine acid phosphate; Figure 2 is the tracing obtained with an amorphous tartrate which was 550 times stronger than the histamine salt, and Figures 3 and 4 show that our most powerful tartrates varied in their oxytocic value from 1000 to 1250 times histamine acid phosphate.

It is interesting to note that our tartrate not only induces uterine contractions at these high dilutions of 1:18,750,000 or more (depending upon the sensitivity of the uterus) but also raises the arterial pressure to an appreciable degree in doses of 0.01 mgm. in cats, causes a marked diuresis in rabbits in doses of 0.05 mgm. or less, and also affects in a characteristic manner the respiration both of the dog and the rabbit, more especially in the unanesthetized animal.

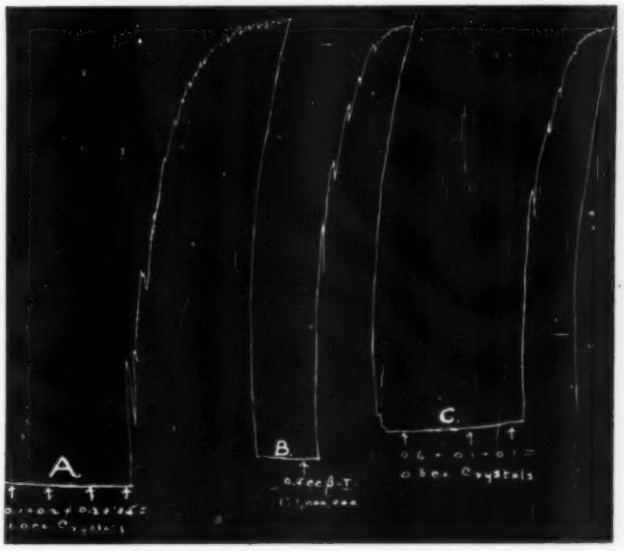

Fig. 1.—Crystalline product 50 to 62.5 times stronger than histamine acid phosphate.

Contraction of the virgin guinea pig's uterus, suspended in 30 c.c. Tyrode solution, produced by a 1:1,000,000 solution of histamine acid phosphate and by a 1:100,000,000 solution of a product consisting of a lump of well formed prisms which crystallized out of a concentrated solution of a pituitary tartrate in pyridine. After one washing with pyridine and then with alcohol-ether (1:20), the lump weighed 4.7 mgm. This product was not recrystallized, as previous experience had taught us that products of this sort did not retain their activity on recrystallization.

A. 1.0 c.c. of crystalline product (0.00001 mgm. or 1:3,000,000,000).

B. 0.5 c.c. of histamine acid phosphate (0.0005 mgm. or 1:60,000,000).

C. 0.8 c.c. of crystalline product (0.000008 mgm. or 1:3,750,000,000).

In proof of this last statement we cite from a protocol of an experiment made on April 13, 1923, in which 0.2 mgm. of our tartrate, with an oxytocic titer of 250 times β-I phosphate, when injected intravenously into an unanesthetized dog weighing 13 kilos, produced the typical effects noted after the administration of the commercial pituitary preparations. Immediately following the introduction of the tartrate a very marked blanching of the skin and visible mucous membranes becomes apparent. A few minutes later the animal begins to have panting respirations at a rate of 60 or more per minute. These are of brief duration and periodic in character, with apnoeic intervals—Cheyne-Stokes in type. This respira-

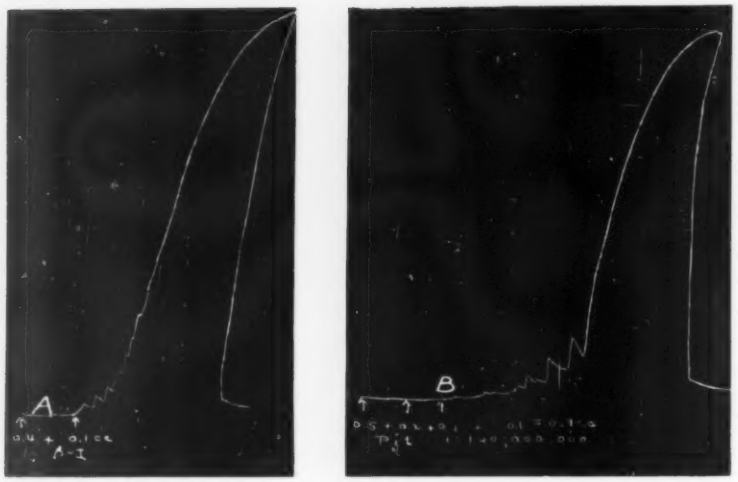

Fig. 2.—Pituitary tartrate 550 times stronger than histamine acid phosphate.

Contraction of the virgin guinea pig's uterus, suspended in 30 c.c. Tyrode solution, produced by a 1:100,000 solution of histamine acid phosphate and a 1:100,000,000 solution of a pituitary tartrate.

A. 0.5 c.c. histamine acid phosphate (0.005 mgm. or 1:6,000,000).

B. 0.9 c.c. pituitary tartrate (0.000009 mgm. or 1:3,300,000,000).

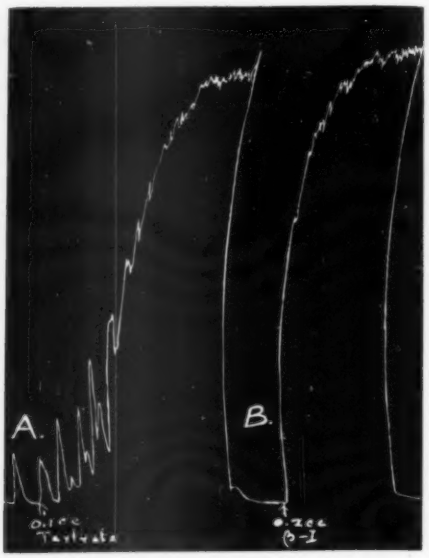

Fig. 3.—Pituitary tartrate 1000 times stronger than histamine acid phosphate.

Contraction of the virgin guinea pig's uterus, suspended in 30 c.c. Tyrode solution, produced by a 1:50,000,000 solution of a pituitary tartrate and a 1:100,000 solution of histamine acid phosphate.

A. 0.1 c.c. pituitary tartrate (0.00002 mgm. or 1:15,000,000,000).

B. 0.2 c.c. histamine acid phosphate (0.002 mgm. or 1:15,000,000).

tory effect of our tartrate on unanesthetized dogs has lately been verified several times. It is in every respect similar to the respiratory effect which was first shown to be characteristic of the action of hypophyseal extracts by Führer and Pankow. These writers very aptly describe the respiratory tracings obtained by them in their experiments in urethane-anesthetized rabbits as "Spindel-form" curves. This striking action on the respiration of unanesthetized dogs does not follow the injection immediately, but only several minutes later, a fact which makes it appear that the effect is of a secondary character, coincident with the very decided and general capillary anemia and dryness of the mouth and mucous membranes which are such striking and immediate results of the intravenous injection of our tartrate and of the commercial pituitary extracts. The experiment just described had for its purpose the study of the effects of our principle on the blood pressure of the unanesthetized dog with Kolls' apparatus. We would remark in this connection that we are dealing with a principle whose action on the circulatory and respiratory apparatus is much more marked in unanesthetized than in anesthetized animals as has been observed in this laboratory by Kolls and Geiling.

Figure 5 illustrates the action of our tartrate in urethane-anesthetized rabbits. It is seen that our active principle induces the same respiratory changes ("Spindel-form" curves) that were obtained by Führer and Pankow with pituitary extracts and later with the "Hypophysin" of the Hoechst chemists.

In reference to the action of our tartrate on the arterial pressure, I would here point out, as I have also done in a series of papers which have come from my laboratory, that this salt is quite free from all preformed depressor substances which are usually mixed with it in the ordinary commercial extracts. As has been stated in the description of the chemical processes, these accompanying depressant substances are completely separated during the early stage of those processes. As a consequence of the absence of depressant substances, the arterial tracing, following an intravenous injection of the tartrate, generally mounts straight upward and does not show that pronounced downward dip which is so characteristic of the tracings obtained with pituitary extracts which have suffered injury in the course of preparation. Even with tartrates of the lower oxytocic titer of say 40 to 75 times β-I phosphate we only rarely find a small downward dip preceding the steep rise in pressure, and it is probable that this finds its cause in too rapid an injection of the solution.

A curious fact, to which I have also called attention repeatedly in my papers on this subject, is the complete inversion of the arterial tracing which so frequently follows upon later injections of the tartrate. I have named this effect the "inversion effect." It is not invariably obtained; the same solution may give the effect in one ani-

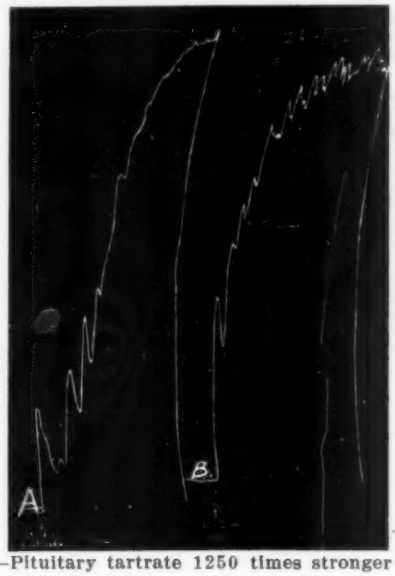

Fig. 4.—Pituitary tartrate 1250 times stronger than histamine acid phosphate.

Contraction of the virgin guinea pig's uterus, suspended in 30 c.c. Tyrode solution, produced by a 1:250,000,000 solution of a pituitary tartrate and a 1:100,000 solution of histamine acid phosphate.

A. 0.4 c.c. pituitary tartrate (0.0000016 mgm. or 1:18,750,000,000).

B. 0.2 c.c. histamine acid phosphate (0.002 mgm. or 1:15,000,000).

With a more sensitive uterus, such as that used in the tests illustrated in Fig. 1, with which only 0.0005 mgm. histamine acid phosphate was required to produce a vigorous contraction, probably only 0.0000004 mgm., or 1:75,000,000,000, of this powerful tartrate would have produced an equally strong contraction.

mal and not in the next. It appears to depend upon a number of indeterminate factors such as the depth of anesthesia, the relative size of the first and subsequent doses, the number of and time interval between successive injections, and possibly the age of the animal. I cannot believe that this inversion effect can be explained by assuming that the tartrate is a mixture of two substances, one possessing a pressor and the other a depressor action, and that the action of the latter becomes manifest only when the vascular apparatus can no longer respond to the former. Against this view the following facts may be adduced. The purified pressor substance, as I have frequently pointed out, is easily injured by various chemical procedures so that its characteristic action is lost and a depressor effect appears in its place. Now in cases where the injury is only partial, that is to say, long before all of the pressor substance has been destroyed, a preliminary depressor effect is obtained—an effect which is apparently proportional to the amount of the pure pressor substance which has been inverted. So also if a very small amount only of histamine (something above an inoperative minimum) be added to our pure tartrate, its

Fig. 5.—Effect of pituitary tartrate (50 × β-I phosphate) on the respiration and blood pressure of a urethane-anesthetized rabbit. Rabbit: Weight 2 kg. Urethane, 1.5 grams in 15 c.c. sub-cut. "A": Injection of 1 c.c. (0.3 mg.) of pituitary tartrate. Upper tracing, respiration; middle tracing, blood pressure; lower tracing, time in seconds.

presence is always detectable by the fact that the arterial tracing shows, when this mixture is injected, a definite downward dip before the rise. There are other points in connection with this phenomenon which need not be taken up here and which have been discussed in earlier papers. I shall give here only one tracing (Figure 6) which illustrates the character of the pressor action and

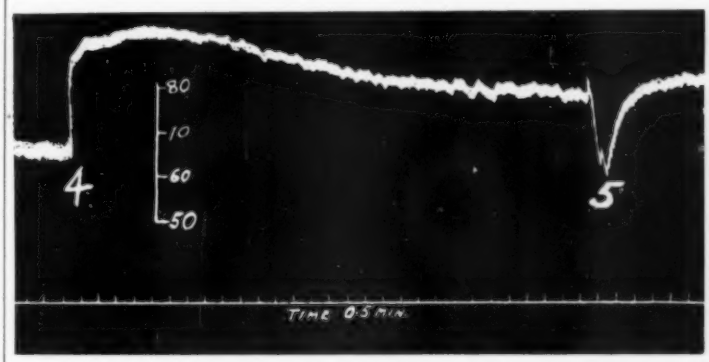

Fig. 6.—Cat, female, weight 2.8 kgm. Ether anesthesia. Carotid blood pressure.

Pressor and inversion effect of an impure tartrate fraction which was thrown out of *n*-butyl alcohol by dropping into it a solution of the tartrate in 93 per cent ethyl alcohol. The oxytocic value of this fraction was 40 to 50 times β-I phosphate.

At (4) 0.5 c.c.(=2.95 mgm.) was injected intravenously. This injection, however, was preceded at intervals by three injections of 1 c.c. each of Armour's pituitary extract, diluted 1:100, without causing an inversion. The pressor effect, therefore, of the tartrate was much smaller than would ordinarily be the case.

At (5) a second and much larger dose, 2 c.c.=8.75 mgm., of the tartrate was injected intravenously and this induced an inversion effect on the blood pressure as shown in the figure. This tracing is quite similar to many that Abel and Nagayama, and Abel and Rouiller obtained with preparations which were made in an entirely different manner, e.g., a phosphate and a tetranitroaniline compound.

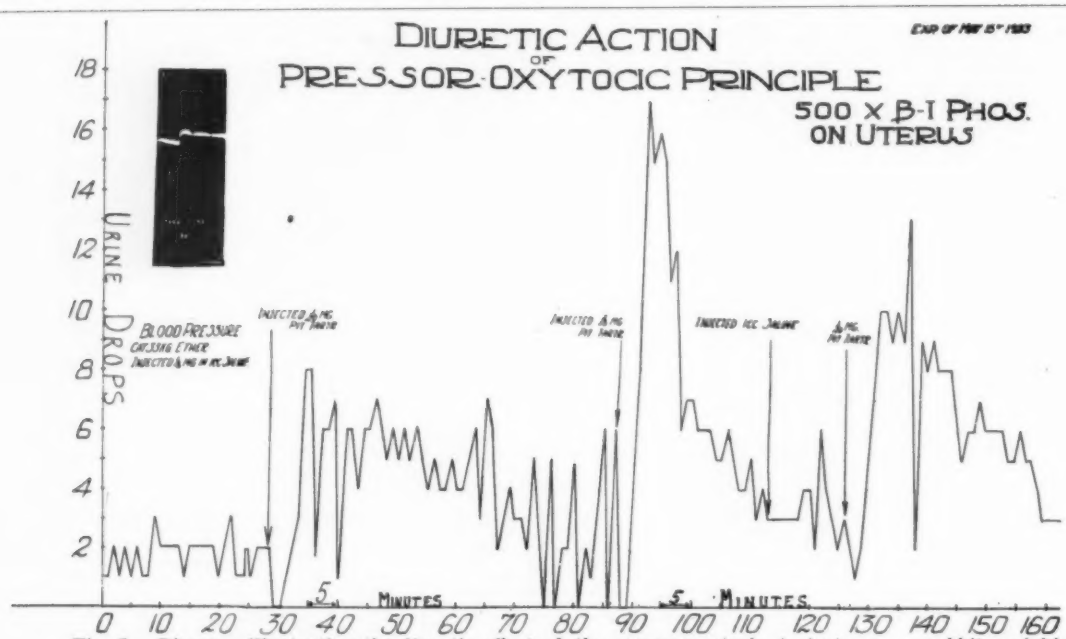

Fig. 7.—Diagram illustrating the diuretic effect of the pressor-oxytocic tartrate on a rabbit weighing 2.5 kgm. The animal had been fed with greens for a week previous to the experiment. Urethane introduced by stomach tube was employed as the anesthetic. The urethra was tied off and the bladder was cannulated with a small glass funnel firmly tied in place and practically replacing the organ, but allowing free communication with both ureters. The oxytocic value of this tartrate is 500 times β-I phosphate.

The upper left hand corner of the chart contains a blood pressure tracing obtained by injecting 0.2 mgm. of the tartrate into a cat weighing 3.3 kgm.

The above diagram illustrates the effect of injecting 0.05 mgm. of the pituitary tartrate. It will be noted that there was a cessation of the flow of urine, or at least a diminished output, for a period of three minutes immediately following the injection. Thereafter a very marked diuresis occurred.

also the inversion effect produced by a tartrate with an oxytocic titer of only 40 to 50 times β-I phosphate. Examples of the same sort of tracings, however, with a tartrate of a very much higher degree of purity can be found in my papers. We may add here that it may happen that the same tartrate gives a good inversion effect on one animal and does not give it on a second animal for reasons unknown to us at present.

Diuretic action. Schafer and his coworkers, Magnus and Herring, discovered the diuretic action of extracts of the pituitary gland and localized this action in the pars intermedia and posterior part of the gland. There has been much controversy in regard to this property of pituitary extracts, and while I cannot here review the work of the various authors on this subject, I would, however, state that on the basis of our own investigations I must hold that our tartrate (and properly prepared extracts of the posterior lobe in general) has an undoubted diuretic action in the green-fed, properly prepared, urethane-anesthetized rabbit. My collaborators and I also hold that it is this diuretic substance itself which acts as a powerful *antidiuretic* for rabbits under the proper experimental conditions and that it is this substance likewise which acts as the *antidiuretic* principle in diabetes insipidus. Even in the green-fed rabbit, as our experiments show, the diuresis is preceded by a temporary cessation of urinary flow. Figures 7, 8 and 9 show that our tartrate, when intravenously injected into properly prepared rabbits, is a rapidly acting and powerful diuretic but one of short duration only. When the effect of a particular dose disappears and the kidney has returned to its normal rate of secretion, a second injection induces diuresis as before and it would appear that this effect can be obtained as often as may be desired. The kidney, in contradistinction to the vascular apparatus as a whole, does not become tolerant to repeated injections of the drug. I desire in this connection to call attention to a striking fact which is brought out in Figures 8 and 9. In Figure 8 it is shown that there is an entire absence of diuresis after the injection of a solution of the tartrate which has been boiled for one half hour under a reflux condenser with 0.5 per cent hydrochloric acid. So too in Figure 9 it is shown that the diuretic action of the tartrate was practically obliterated after exposure of its solution to normal sodium hydroxide for one hour at room temperature. It has already been stated that treatment with alkali completely abolishes every known physiological action of the pituitary tartrate and that the above treatment with acid is equally drastic in its effects with the exception that the oxytocic property of the salt is not so completely abolished as in the treatment with alkali.

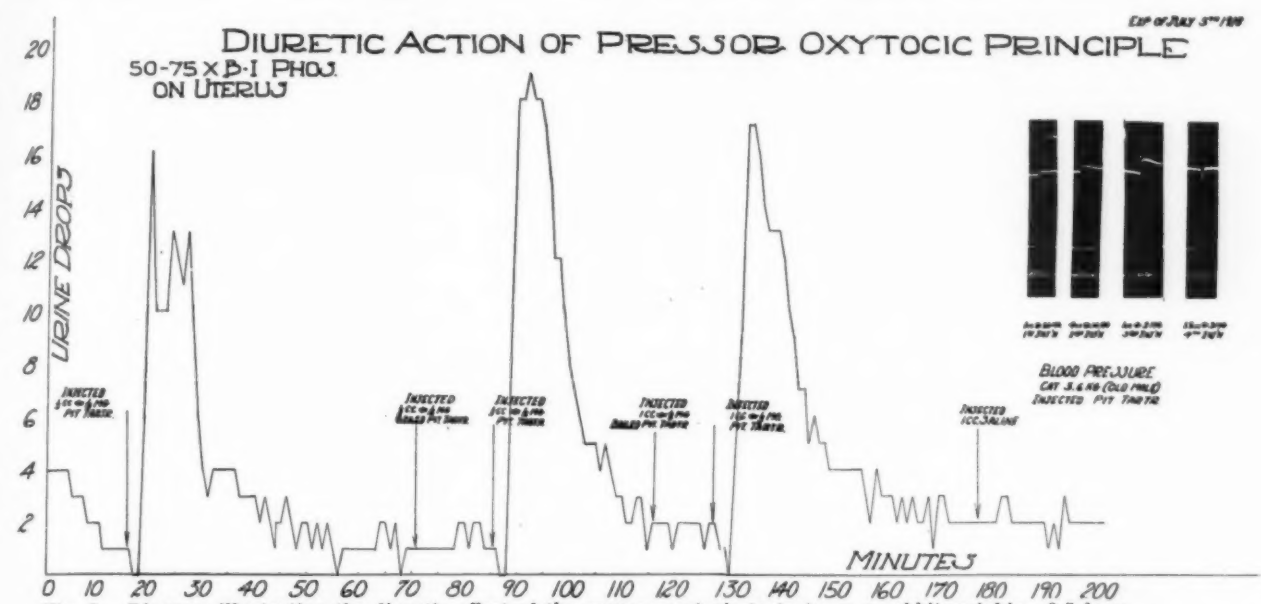
DIURETIC ACTION OF PRESSOR OXYTOCIC PRINCIPLE
50-75 X β-I PHOS.
ON UTERUS
URINE DROPS
MINUTES
BLOOD PRESSURE
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

Fig. 8.—Diagram illustrating the diuretic effect of the pressor-oxytocic tartrate on a rabbit weighing 2.5 kgm.

The animal had been fed with greens for a week previous to the experiments. Urethane introduced by stomach tube was employed as the anesthetic. The urethra was tied off and the bladder was cannulated with a small glass funnel firmly tied in place and practically replacing the organ, but allowing free communication with both ureters. The oxytocic value of this tartrate varied from 50 to 75 times β-I phosphate.

The upper right hand corner of the chart contains four small tracings showing the pressor effect of the tartrate and the inversion effect on the fourth injection.

From the above diagram it will be seen that there is a cessation of urine flow which lasts for about three minutes immediately following the injection of the pituitary tartrate. Thereafter a very striking diuresis occurs, the urine now being pale in color. Note the entire absence of diuresis following the injection of a solution of the tartrate which has been boiled for one-half hour under a reflux condenser with 0.5 per cent HCl.

Antidiuretic action of the tartrate in diabetes insipidus. Von den Velden appears to have been the first to have made the important discovery that the administration of pituitary extracts *sub cutem* to normal individuals as well as to patients suffering from chronic renal disease causes the kidneys of both these classes of individuals to secrete less urine and of higher specific gravity. This author also found that the antidiuretic action of the extract was especially efficacious in a case of diabetes insipidus nervosus. His patient obtained immediate, if only temporary, relief from the distressing symptoms. Coincidently Farini related the case of a girl, aged twenty-three, suffering from marked diabetes insipidus, who was successfully treated by him with subcutaneous injections of pituitary extracts. The further and very extensive literature bearing on this use of pituitrin in diabetes insipidus, as well as that dealing with the surgical lesions of the gland in relation to experimental polyuria (Cushing and his coworkers) and also that dealing with the relation of clinical disorders of the pituitary to diabetes insipidus cannot be taken into consideration in this lecture. One fact emerges very clearly from the great amount of experimental work that has been done since the appearance of the earlier papers on this subject and that is that the diuretic effect produced by pituitary preparations in experiments on animals is of transient duration and that the really characteristic and more important action of these preparations on normal human beings as well as on those afflicted with diabetes insipidus is antidiuretic. Our own work seems to show that the transient diuretic action of our tartrate on green-fed, urethane-anesthetized rabbits may apparently serve as a means of gauging its antidiuretic activity in diabetes insipidus, though undoubtedly the pressor action of the salt would be a better index of its antidiuretic action, inasmuch as the lowering of the urinary output seems to depend largely, if not entirely, on the vaso-motor action of the drug.

Through the kindness of Professor L. G. Rowntree of the Mayo Clinic, of Dr. A. M. Snell of the Mankato Clinic and Drs. McCann and Keefer of Professor Longcope's clinic and Dr. Bugg of Professor Howland's clinic, we were placed in a position to test our tartrate on four patients suffering from primary diabetes insipidus. The tartrates employed were not of the highest degree of purity. They ranged from 50 to 75 times β-I phosphate in the therapeutic trials at the Mayo Clinic to 160 times β-I phosphate at the Hopkins Hospital trials. All of the

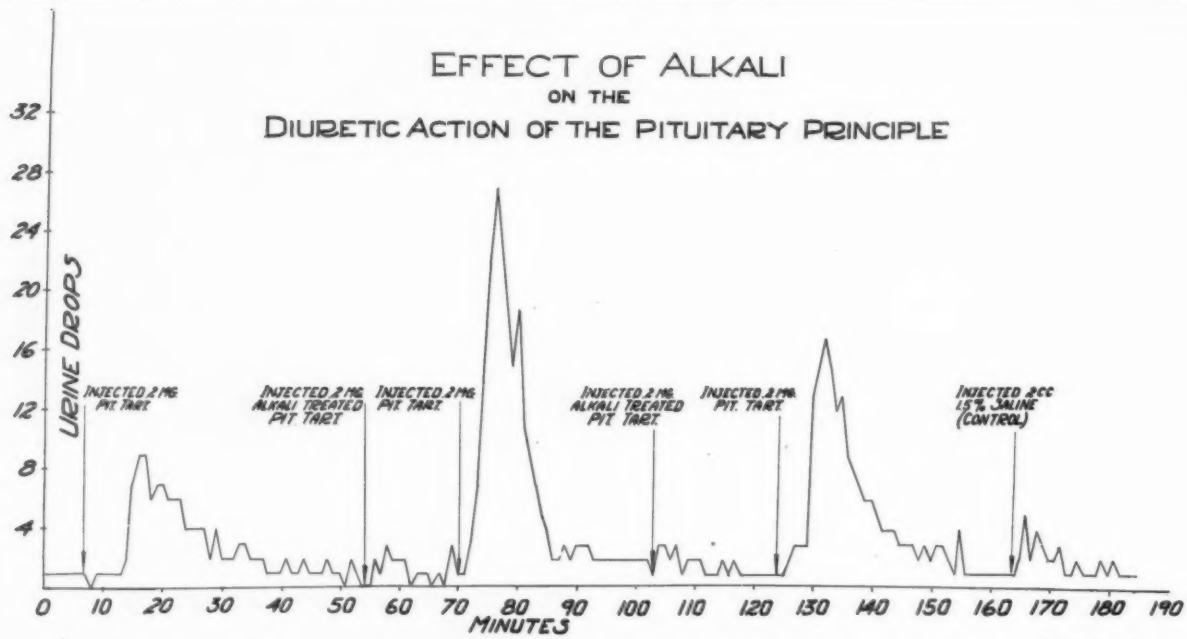

Fig. 9.—Diagram illustrating the destruction of the diuretic action of the pituitary tartrate by subjecting it to normal NaOH for one hour at room temperature.

A rabbit weighing 2.8 kgm. and which had been fed greens for one week previous was used as the experimental animal. Anesthesia was induced by urethane given subcutaneously. The urethra was tied off and the bladder cannulated with a small glass funnel firmly tied in place and practically replacing the organ, but allowing full communication with both ureters.

The pituitary tartrate used for this experiment is the same as that employed in experiments illustrated in Fig. 8.

It will be noted from the chart that the diuretic action of the pituitary tartrate was practically obliterated after treatment with normal sodium hydroxide for one hour at room temperature. The control injection of 2 c.c. of 1.5 per cent saline gave a somewhat greater effect than the alkali-treated pituitary tartrate.

clinical and therapeutic data bearing upon these trials are given in detail in a paper by Abel and Geiling, and a perusal of that paper will, I think, convince the reader that our tartrate possesses the characteristic antidiuretic property for diabetes insipidus in equal measure with that exhibited by the ordinary commercial pituitary extracts. Although the tartrate used in these clinical trials did not have the highest oxytocic value, as unfortunately none of the more purified salt was at our disposal at the time, I cannot believe that the results would have been any different had the purer tartrate been used, such, for example, as the one whose oxytocic titer is 500 times β-I phosphate and the diuretic action of which is so well illustrated in Figure 7. The less pure tartrates have been shown in my laboratory to contain as contaminating substances only crystalline salts which are entirely devoid of physiological properties, and this is the reason that the only difference which we have found in our work with these tartrates is one not of a qualitative but of a quantitative character. That is to say, the purer the tartrate the less is required of it for the production of any given physiological effect whether it be antidiuretic or oxytocic in its nature. It would appear, therefore, that our tartrate possesses the antidiuretic property of the posterior lobe extracts to the same extent that it exhibits all of the other characteristic physiological properties of such extracts—oxytocic, cardiovascular and respiratory—which have been discussed in this lecture.

Is the Posterior Lobe Principle with its Manifold Physiological Actions a True Hormone?

Having shown that the principle under discussion is one of extraordinary potency and possessed of a variety of physiological actions, the question that now arises and demands attention is—is this product a true hormone, a principle of internal secretion which finds its way ultimately into the general circulation and from there to various organs? Anatomists and histologists all admit that it is quite possible for an active principle to find its way into the circulation from the posterior lobe either by way of the perivascular lymph channels into the cerebrospinal fluid and from there into the venous sinuses, or by way of the absorbing blood capillaries directly into the circulation. The histological structure of the pars posterior apparently gives no support to the belief that an active principle is produced in this part of the hypo-

physis; in a word, there is no positive anatomical evidence that an internal secretion is formed in the posterior lobe itself. The theory that the active principle of the posterior lobe is really derived from the pars intermedia was first advanced by Herring in 1908, on the basis of extensive histological studies of the mammalian pituitary body, and the theory met with favor on the part of Houssay and others. Herring describes groups of cells belonging to the pars intermedia which penetrate the posterior lobe, and he suggests that these cells furnish a secretion in the form of colloidal globules or masses which supply the active principle to the pars posterior. This view, however, is not generally accepted. Many critics, as Bremer and Bailey, suspect that this colloidal material does not represent an active product but is merely the result of cell degeneration.

Schmidt and May are often cited as having furnished evidence that an antecedent of the posterior lobe principle is contained in the tethelin of Robertson. E. Leschke, quite independently of these authors, also makes a similar suggestion and on similar grounds. Schmidt and May found that when tethelin is treated with barium hydroxide the resultant break-down products cause contraction of the guinea pig's uterus and also induce a slight rise of blood pressure. From these observations they conclude that the active principle of the posterior lobe finds its chemical precursor in the anterior lobe. Now tethelin, as we have seen, is not a chemical individual, and arguments derived from such experiments as those made by Schmidt and May and by Leschke have to my mind no necessary bearing whatever on this question. The split products of all sorts of tissue elements which are in no way related to the pituitary principle easily give a small effect on the guinea pig's uterus.

One is not justified in taking it for granted that the principle under discussion cannot arise in the posterior lobe itself. A substance of such extraordinary potency need only be produced in very minute quantities even in times of emergency. As Cowdrey remarks in another connection, the absence of visible secretion antecedents in the cells of a structure may mean very little, for he points out that an active and necessary constituent is produced in the anterior lobe of young tadpoles, for example, in an early stage before evidence of cell differentiation makes its appearance. While the experiment neither strengthens nor weakens the supposition that the neural tissue of the posterior lobe cannot or does not itself produce an active principle like the one under discussion, it may be stated in this connection that Dr. Geiling and I recently made extracts from a gliomatous tumor, immediately after its removal from the skull of a patient by Dr. Dandy, and found that this extract gave no evidence of containing the blood-pressure-raising principle. The only obtainable effect on the blood pressure was the marked depressor action which is so characteristic of extracts of cerebral tissue.

Professor Dixon of Cambridge has within a few months past made the claim based on very convincing experiments of his own that the cerebro-spinal fluid of dogs always contains a small amount of a plain muscle (uterine) stimulating substance which he believes to be derived from the posterior lobe. He finds that, after total extirpation of the hypophysis, some of this principle is still contained in the cerebro-spinal fluid. When, however, an extract of the posterior lobe is injected intravenously into a normal animal, he discovers that the cerebro-spinal fluid contains a greatly increased amount of the uterine stimulant. He concludes that this enrichment is not due to a direct passage of the injected posterior lobe principle from the blood vessels into the cerebro-spinal fluid but that it is due to the fact that the injected active principle stimulates the hypophysis to secrete an increased amount of the principle. This action, as Dixon says, would be perfectly analogous to that which is seen when an injection of bile salts causes the liver to secrete more bile and more bile salts.

Certain earlier observers have obtained results with cerebro-spinal liquor which are not in agreement with those of Dixon. Thus, C. and M. Oehme state that with the normal, unconcentrated cerebro-spinal fluid of laboratory animals they could obtain no distinct evidence of any action on the uterus of the guinea pig. They consider the uterine test as one that is not sufficiently sensitive for the detection of an oxytocic stimulant in this fluid, as it was only after the addition of as much as 10 c.c. of the cerebro-spinal fluid to the uterine bath containing 60 to 80 c.c. of Ringer's solution that an occasional minimal reaction could be obtained. It should be stated, however, that while these authors could obtain no satisfactory evidence of the existence of an oxytocic principle in normal cerebro-spinal liquor they nevertheless claim that a vaso-constricting substance or substances are present in this fluid. They rest their claim on perfusion experiments with the surviving rabbit ear (Krawkow-Pissemsky method), in which a very marked diminution in the outflow was observed when centrifugalized lumbar-puncture fluid was employed as the perfusion liquid. The observed vaso-constricting action was surprisingly large, being equal to that obtained with a commercial pituitary extract when diluted 1:10,000 to 1:20,000. It need hardly be pointed out that this extraordinary observation cannot be brought into agreement at the moment with the experiments of others in regard to the hemodynamic action of cerebro-spinal liquor. It should also be noted that the Oehmes state clearly that their biological tests are inadequate for the identification of the assumed vaso-constricting principles.

Leschke must also be named among experimenters who state that they have never obtained any evidence of the existence of an oxytocic principle in cerebro-spinal fluid. Dixon states that the cerebro-spinal liquor varies greatly

in its content of the oxytocic principle. He has seen as little as 10 drops of normal cerebro-spinal fluid produce a decided contraction of the uterus, but finds that the usual amount required to elicit an effect is 3 or 4 c.c., and that occasionally even larger amounts are inactive. May it not be, then, that the negative results of the Oehmes and of Leschke in respect to the oxytocic evaluation of cerebro-spinal fluid are explainable on the assumption that, making fewer observations than Dixon, these authors happened upon a larger percentage of cerebro-spinal fluids which contained only very little of the uterine stimulant?

Trendelenburg has recently confirmed Dixon's results, with the exception, however, of finding that 1 c.c. of the cerebro-spinal fluid of cats corresponds in its action on the surviving uterus of rats and guinea pigs to only 1/35000 mgm. of fresh posterior lobe tissue as against Dixon's highest oxytocic evaluation of 0.2 to 2 mgm. for 1 c.c. of the cerebro-spinal fluid of the dog. Trendelenburg finds that the cerebro-spinal fluid of cats produces contractions of the guinea pig's uterus even when diluted fivefold and that its activity is very much decreased twenty-four hours after transecting the stalk of the pituitary gland.

It would appear, then, that the cerebro-spinal fluid of animals contains an oxytocic principle, but before it can be definitely accepted that this oxytocic principle is identical with that found in the pars intermedia and posterior lobe of the hypophysis, additional experimental evidence must be adduced. This is absolutely necessary in view of our demonstration that the posterior lobe contains only one specific hormone which has blood pressure raising, antidiuretic, respiratory and other physiological actions in addition to its oxytocic action.

Now, in respect to the hemodynamic action of normal cerebro-spinal fluid there has been much controversy. The latest paper on this subject is that of C. Jacobson, which also takes into account the work of earlier experimenters (Cushing and Goetsch, Carlson and Martin). This author concludes, on the basis of a large number of blood pressure experiments made with human and bovine cerebro-spinal fluids, that "the effect is essentially a depressor one instead of a pressor one indicative of the posterior lobe secretion."

The only experimenter who, as far as I am aware, has studied the effect of the cerebro-spinal fluid on the function of the kidneys is E. Leschke. This author states that he has not been able to obtain the slightest evidence of the presence of an antidiuretic principle in cerebro-spinal fluid after the injection of 20 to 30 c.c. of the fluid into normal human beings who have taken a liter and a half of water early in the morning on an empty stomach. This negative result need occasion no surprise when it is reflected that one could hardly expect an antidiuretic effect from the few millionths of a milligram of the active principle which, as I calculate from Trendelenburg's data, is all that would be present in so small a quantity as 20 to 30 c.c. of cerebro-spinal fluid. It would, in my opinion, be necessary to work up much larger quantities of the cerebro-spinal fluid and attempt a rough isolation of the oxytocic principle in order to obtain enough of it to make worth while antidiuretic tests on the human being. I have calculated, on the basis of therapeutic trials with our tartrate, that it would require around 1/100 mgm. of a tartrate with an oxytocic titer of 1250, administered subcutaneously, to give in a case of human diabetes insipidus the usual antidiuretic effect lasting three or four hours.

Much, therefore, as I should like to accept without reservation the conclusion of Dixon, fortified, as it now is, by the corroborative experiments of Trendelenburg, I must nevertheless point out that its correctness will not remain unchallenged as long as it has not been demonstrated that the above named physiological actions of the posterior lobe hormone are exhibited by the cerebro-spinal fluid in addition to its oxytocic action.

In 1915, Weed and Cushing observed that intravenous injection of a post-pituitary extract into dogs, cats and rabbits increased the outflow of cerebro-spinal fluid from a calibrated catheter introduced into the third ventricle or into the subarachnoid cistern. Dixon and Halliburton contend that the pituitary extract induces marked contraction of the bronchi with the consequent appearance of asphyxia and to this abnormal state of the animals, in the experiments of Weed and Cushing, the increased outflow of cerebro-spinal fluid is ascribed rather than to an increased fluid production by the choroid plexuses as a result of a stimulating action of the pituitary principle. For a full discussion of the present status of this controversy and of the more recent publications on the action of certain well-known pharmacological agents and of tissue extracts on the cerebro-spinal fluid pressure, I would refer to Weed's comprehensive review on the cerebro-spinal fluid in *Physiological Reviews* for 1922.

As it has not been demonstrated to a certainty that the pars intermedia and the posterior lobe secrete into the cerebro-spinal fluid, may it not be worth while to consider whether the active principle does not find its way directly into the blood stream by way of the capillaries of the posterior lobe? With a view to testing this hypothesis my associates, Drs. Dandy and Geiling, and I are at the moment engaged in comparing the oxytocic and pressor values of blood drawn from the sinus intercavernosus of dogs (the sinus which receives the venous blood of the hypophysis) with that drawn at the same time from a peripheral vein. At the time of writing no conclusive data have been obtained, as we have found that the bloods thus far drawn are highly toxic for the surviving uterus, presumably because of their high content in ether, this being the anesthetic employed by our

colleague Dandy in the performance of the surgical operation. To obviate this complication we are now allowing the animals to recover from the trephining operation and we purpose some days later to abstract blood from the sinus intercavernosus and from a peripheral vein without the use of any anesthetic whatever—a procedure which we regard as quite feasible when undertaken with docile animals. It is also possible that the active principle under discussion finds its way in part into the cerebrospinal fluid and in part into the blood capillaries of the posterior lobe.

What evidence has experimental surgery to offer in favor of the view that the posterior lobe principle acts as a hormone in the higher animals, quite aside from the manner in which the principle finds its way into the blood? Without going into details it may be said that practically all experimenters agree in stating that the posterior lobe can be removed in the higher animals, as dogs, for example, without danger to life, without, indeed, inducing symptoms of any kind, providing only that no injury has been done to the contiguous parts of the floor of the third ventricle. In the case of the lower animals, however, as in the amphibia, very different and quite unexpected results have been obtained in recent years. A large number of workers, to name only Adler, Gudernatsch, P. E. Smith, Allen, Atwell, Swingle, Hogben and Winton, Pendé and Uhlenhuth, have shown conclusively that one or both lobes of the hypophysis may be removed completely, either from adult amphibia or from the larval forms, without injury to the contiguous portions of the brain. Leaving out of consideration the results of ablation of the anterior lobe, the concordant experiments of all these investigators prove that the posterior lobe provides an internal secretion in the amphibia which plays a decisive rôle in controlling the pigmentary responses of the skin. Adult frogs (or tadpoles) remain pale after complete hypophysectomy or after removal of the posterior lobe alone, the tadpoles in such cases being termed albinos (P. E. Smith). These pale frogs or albinic tadpoles serve as an extremely delicate indicator for the post-pituitary secretion. Hogben and Winton, in extensive observations some of which were in confirmation of the findings of workers in this country, note that the injection of extracts of the pars intermedia-pars posterior of the pituitary gland of mammals, birds, reptiles, amphibia and fishes causes the melanophores of hypophysectomized pale frogs to expand to a maximum in about twenty minutes to half an hour, thus restoring their dark appearance. Addition of an ordinary commercial posterior lobe extract to the water in which albinous tadpoles are swimming also soon causes them to assume the deeply pigmented appearance of normal tadpoles. Through the kindness of Dr. Swett of the Anatomical Institute of this University we were put in possession of a number of such hypophysectomized or albinous tadpoles and it was easy for us to show that the addition of a minute amount of our tartrate to the medium in which the tadpoles were living caused their melanophores to expand as promptly and effectively as did the addition of an aqueous extract of the posterior lobe.

A beautiful and striking experiment showing this expansion of the melanophores is the following:—A frog is placed in a white porcelain receptacle covered with a glass plate and exposed to a strong light for six or more hours, as advised by Hogben and Winton, until it turns into a pale frog, or one whose melanophores are contracted to an extreme degree (pale frog). A pale frog of this sort is decapitated, both hind legs are ligatured just below the knee-joint and then severed from the body. A drop or two of a saline solution of pituitary tartrate with an oxytocic titer of 160 times β-I phosphate and containing 0.016 mg. per 0.1 c.c. is injected underneath the skin close to the plantar surface of the foot near the cruro-tarsal joint, and by gentle manipulation the fluid is worked down into the lymph sacs surrounding the toes. The web of the foot is now expanded over a pledget of cotton, placed on a large watch glass and examined under a low power of the microscope. The other leg is injected with an equal volume of normal saline at the same site as mentioned above, and this is examined under a second microscope. Corresponding areas of the skin over the toes of the two feet, or of the web of the feet are selected for comparison. Before injection, the skin melanophores of both feet are, generally speaking, seen only as small circular black spots, but in a few minutes the most striking difference is observed; the melanophores of the foot which has been injected with the pituitary tartrate begins to expand in a "reticulate" or stellate manner. The expansion attains a maximum in about 20 minutes. The foot injected with saline shows no change whatever, the melanophores having remained in their previous state of extreme contraction. The difference between the two feet is also visible to the naked eye, the skin of the foot injected with pituitary tartrate being much darker. These experiments were carried out at a room temperature of 84° F. The effect on the melanophores of the frog's foot in the above experiment was so rapidly obtained and was so very pronounced that there can be no doubt that the solution was needlessly strong, and that marked expansion of the melanophores would be equally well obtained with much weaker solutions.*

* These preliminary experiments on hypophysectomized tadpoles and on the frog's foot were made only with relatively impure preparations of our tartrate and whether the action on the melanophores was due to the pressor-oxytocic-diuretic principle or to an admixed impurity will have to be determined by using the most highly purified salt. It also still remains to be determined if the melanophore-expanding action is destroyed by acids and alkalies as are the other physiological properties of our principle.

It may be stated in this connection that I am fully aware that most experimental zoologists refer the production of the melanophore-expanding agent in the amphibia to the pars intermedia. There is, however, a sharp difference of opinion among them when it comes to the action of the bovine post-pituitary extracts employed in medicine which are in reality extracts of the pars intermedia plus pars posterior. P. E. Smith, for example, states in a footnote that the immersion of larvae in pituitrin (Parke, Davis and Co.) "has produced neither constant nor pronounced changes in the pigmentary system even when used in strengths sufficient to cause the serious distress or death of animals." Hogben and Winton, on the other hand, invariably obtained expansion of melanophores under all circumstances with very small doses of the liquid sterile posterior lobe extract "Infundin" (Burroughs, Wellcome). In view of their results Hogben and Winton state that they are able "for the first time to bring the results of hypophysectomy into harmonious relation with the effects of pituitary administration." May not the negative results of Smith be due to the chloretone which is present in the pituitrin of Parke, Davis and Co.? Both of the commercial preparations here named are extracts of the pars intermedia plus pars posterior, as already stated. It would seem that the positive results of Hogben and Winton, based on an extensive and well-controlled series of experiments, are the more acceptable for the present. These authors appear to take it for granted that it is the pars intermedia of the pituitary gland of the amphibia which has the specific action on the melanophores. I find no record of any experiments made by them in which the melanophore-expanding agent is localized either in the pars intermedia or pars posterior or in both in the higher animals. Smith, in the footnote referred to above, says: "an emulsion of the posterior lobe (less the pars intermedia), even when used in strengths greatly in excess of that employed with the pars intermedia, appears not to evoke this reaction."

There are no doubt other functions of the posterior lobe in the amphibia which are as yet unknown and the absence of which, like that seen when the specific local action on the melanophores is abolished, is not incompatible with a continued existence. At any rate, we find in these experiments on amphibia and in this striking example of substitution therapy by our tartrate, as well as by post-pituitary extracts, clear proof that in these animals the posterior lobe secretes a true hormone into the blood which exerts an influence on cellular structures which are far removed from the hypophysis.

Are we to conclude from the negative results of ablation of the posterior lobe in the higher animals that this part of the hypophysis (inclusive of the pars intermedia) plays no rôle whatever in the economy of these animals; that it is entirely without any physiological significance? To draw such a conclusion from these experiments is entirely unjustifiable. I am quite prepared to believe that the entire hypophysis can be removed from the adult dog without inducing permanent alteration of any kind in the animal, but I am not prepared to admit that an operation of this nature results in the removal of every remnant of tissue exhibiting hypophyseal functions. Let us confine ourselves for a moment to a consideration of posterior lobe ablation alone. It is easy to demonstrate that the ordinary so-called complete extirpation of the hypophysis or of the posterior lobe in the higher animals fails entirely to remove all tissue that has the pharmacodynamic properties of the posterior lobe. Dr. Geiling and I have repeatedly made the following experiment, full details of which will soon be published. We have removed the entire brain of the dog and of the sheep immediately after death, transecting the hypophyseal stalk carefully and with the employment of as little traction as possible. The brains are then placed bottom upward, the cut hypophyseal stalk is carefully elevated with pincers and then transected with small sharp scissors so close to the brain that a depression is left in the base of the brain with an opening into the third ventricle. In a word, the stalk is removed together with some of the contiguous tissue comprising the floor of the third ventricle. Dr. Dandy, who has personally observed these manipulations, assures us that in no instance of experimental hypophysectomy does the surgeon so completely remove the upper portion of the hypophyseal stalk.

A half dozen sheep brains are prepared in this manner, the heads of the animals having been brought still warm from a nearby slaughter-house. On the lower surface of each brain, at the former site of attachment of the hypophyseal stalk, there is now a small cone-shaped depression opening into the third ventricle. We have been mindful of the danger of contaminating the cut surfaces with neural tissue which might possibly be squeezed out of the inner part of the hypophyseal stalk and have for these reasons avoided traction on the stalk, and have even excised along with it a small portion of the adjoining hypothalamus, as already stated.

The next step consists in the careful removal of the tissue immediately surrounding the site of the upper end of the removed hypophyseal stalk. Anteriorly, in this dissection, some of the soft tissue covered by the optic chiasma is removed and posteriorly a part, if not all, of the tuber cinereum is included. The amount of brain tissue thus dissected out from six prepared sheeps' brains varies from 0.2 to 0.4 gram. It is immediately ground up with a few cubic centimeters of a 0.25 per cent solution of acetic acid, brought to a boil and filtered. The intravenous administration of 0.5 c.c. of this extract, representing only 0.03 gram of hypothalamus tissue, induces a dis-

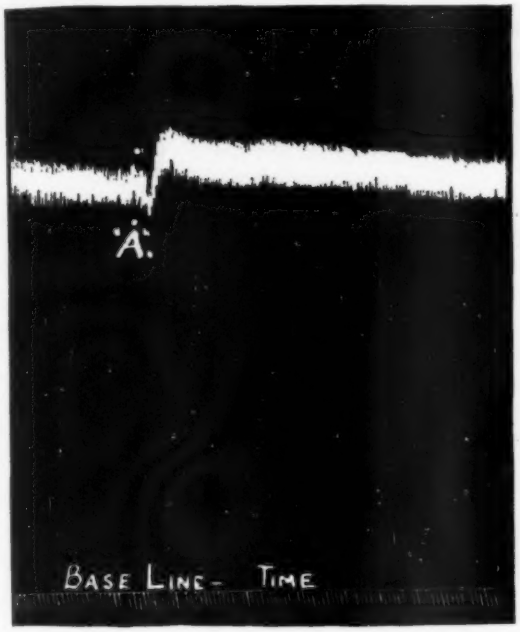

Fig. 10—Blood pressure tracing obtained after the intravenous administration of 0.5 c.c. of extract, representing 0.03 gm. of hypothalamus tissue, into a urethane-anesthetized cat.

tinct rise of the arterial pressure in a urethane-anesthetized cat, as may be seen from Figure 10. Naturally, the injection of somewhat larger quantities gives a correspondingly increased effect on the blood pressure. This extract also stimulates the guinea pig's uterus in a manner characteristic of post-pituitary extracts. We may regard it as demonstrated, therefore, that the tissue of the hypothalamus continuous with the upper end of the hypophyseal stalk contains the posterior lobe hormone. At the moment we are not able to state how this tissue compares in respect to its content of hormone with the posterior lobe itself.

As is well known, extracts of brain tissue in general contain a powerful blood pressure-lowering agent, with absolutely no indication of the presence of a pressor substance. We have in all cases matched our pressor extracts of tissue from the floor of the third ventricle with similar depressant extracts made from the tissues lining the lateral ventricles. These extracts were very active in lowering the arterial pressure and were found to have only a feeble oxytocic action in comparison with that of the former.

Extracts were also made of the posterior part of the hypothalamus inclusive of the corpora mammillaria, and the blood pressure tracings obtained after the intravenous injection of such extracts show them to contain considerably less of the pressor-oxytocic body and much more depressor substance than were found in extracts made from the anterior division of the hypothalamus.

The demonstration by Geiling and myself that there exists in the grey matter in the floor of the third ventricle a tissue which yields an extract possessed of pressor and oxytocic properties, or in other words a tissue capable of elaborating a principle which appears to be identical with that found in the pars posterior and pars intermedia of the hypophysis, supplies me with the necessary data for putting forward an explanation entirely different from that offered by Camus and Roussy for their findings. If these investigators in their experimental hypophysectomies did not remove all of the specific hormone-producing tissue in the anterior hypothalamus —and such was certainly the case in view of our above-named observations—it is not surprising that no polyuria or other signs of posterior lobe deficiency were noted by them. In all so-called total hypophysectomies hitherto performed in adult animals and which were followed by no observable symptoms, the amount of hormone-producing tissue, although constituting only a small fraction of the total posterior lobe material, seems, nevertheless, to have sufficed for the production of the necessary physiological minimum quantity of an antidiabetic substance.

Camus and Roussy, as also Bailey and Bremer, found that puncturing the grey matter in the neighborhood of the tuber cinereum was promptly followed by polyuria in hypophysectomized animals which had not previously shown any symptoms. In experiments of this kind is it not reasonable to suppose that such a puncture (of the floor of the third ventricle in such previously hypophysectomized animals) injured the last remaining portion of hormone-yielding tissue situated in the hypothalamus? Such an explanation of the results obtained by the aforementioned investigators naturally involves the assumption that the posterior lobe and pars intermedia, and the similarly functioning tissue of the grey matter in the hypothalamus, elaborate a hormone which, when present in insufficient amount, leads to the production of polyuria or diabetes insipidus. This pathological condition would on this theory find its explanation in a deficiency of a specific hormone which controls the removal of water and certain electrolytes from the body via the kidneys. Such a theory is quite in opposition to that of Camus and his collaborators and others who explain the polyuria incident to the puncture of the hypothalamus in hypophysectomized animals on the assumption of injury to *hypothalamic nerve centers*. These observers further claim that puncture of the hypothalamus is equally effective in producing polyuria *in animals whose hypophysis has remained entirely untouched*. One would suppose that in this case the apparently uninjured pars intermedia and pars posterior could furnish to the body the necessary amount of the specific hormone needed by it, and hence that the destruction only of the upper and much smaller area of hormone-yielding tissue could not induce polyuria. Before accepting such an explanation, it would have to be

shown that puncture of the hypothalamus in the immediate neighborhood of the upper attachment of the hypophyseal stalk in no wise interferes with either the production of the hormone in the pars intermedia or pars posterior, or with its transference to the cerebro-spinal fluid or to the blood stream or to both. It is a curious fact that in frogs a puncture of the brain, trifling in itself and followed by no observable symptoms, can nevertheless be shown to have caused certain profound alterations in the response of the frog's brain and spinal cord to a whole series of sulphonated convulsant dyes. In past years my collaborators (Syz and others) and I have found that various trifling experimental lesions of the frog's brain cause this organ to take up such dyes in great abundance, and convulsions are produced in these animals by doses very much smaller than would be required to produce the same symptoms in normal animals. Furthermore, such frogs differ from normal ones in that their brain and spinal cord take and retain a great deal of the injected dyes. It is therefore within the range of possibility that puncture of the hypothalamus is not without an effect on the functional integrity of the pars posterior and pars intermedia.

Dott reports that the placing of a small piece of platinum so that it rests on and irritates the pars intermedia and pars posterior gives rise in the dog to an abundant polyuria—1200 to 1500 per cent above the normal. He explains this pathological condition by assuming it to be due to an increased secretion of the pars intermedia resulting from a lasting irritative stimulation of that region. Could it not as well be assumed that the effect of the continuous irritation interferes with the production or elimination of the necessary antidiuretic hormone, resulting in a condition of hypo-function?

Perhaps experimental polyuria would follow puncture of the posterior lobe without further injury to the hypophysis. Certainly, a temporary diabetes insipidus is frequently described as being incident to the extirpation of the gland. It is within the bounds of possibility also that an injury to the upper or hypothalamic portion of the neural hypophyseal tissue interferes more markedly with its functions, for reasons broached above, than one of the pars posterior.

I have thrown out the above suggestions because the underlying assumption is in agreement with the known facts of physiology. A small part of the liver, a fraction of the insular tissue of the pancreas (one fifth), one parathyroid glandule out of four, may, in each instance, suffice to carry on the functions of the gland, although four-fifths or more of the glandular tissue in question may have been destroyed by disease or removal in an experiment.

To recapitulate, I feel confident that further research will demonstrate as satisfactorily for the higher animals as for the amphibia that the posterior lobe with the pars intermedia and the similarly functioning tissue of the hypothalamus elaborates a specific hormone which controls the removal of water from the body via the kidneys and perhaps other organs. Is it an entirely untenable supposition that a deficiency of this hormone should lead to a polyuria or diabetes insipidus?

This theory finds strong support in the opinion of clinicians like Frank and Marañon who have long maintained (Frank since 1910) that there is a causal connection between morbid states of the hypophysis and diabetes insipidus and who therefore class the posterior lobe (or some other division of the hypophysis concerned with the movement of water in the body) with the internal secretory organs. In opposition to these writers, other clinical authorities, Aschner, Leschke and others, have brought forward many facts, both clinical and experimental, which in their opinion show that lesions of the hypothalamic centers are essential, in part at least, in the causation of this disease.

We may ask, in conclusion, what proof we have that the anterior lobe of the hypophysis has any significance for the higher animals and human beings. It has been maintained in the past by a few authorities, such as the clinician, Strümpel, that the gland is a vestigial structure without any present physiological significance for the higher animals. Camus and his collaborators have already been cited as refusing to believe that the posterior lobe is of functional significance. Their skepticism also extends to the anterior lobe. These investigators would set aside the well known clinical entities, gigantism, acromegaly, dystrophia adiposogenitalis, the hypophyseal cachexia of Simmonds and diabetes insipidus, as having no connection whatever with the hypophysis. They believe that all these diseases can be correlated with morbid alterations or with experimentally induced lesions of the hypothalamus. I cannot here enter into the literature of this subject in detail or name those who have given either a partial or their entire support to such views. Bailey has given a careful critical review of the earlier experimental work of Paulesco, Horsley, Cushing and many others, the perusal of which leaves one with the impression that the enormous amount of experimental work that has been done on the higher animals (as the dog, for example) has not led to decisive results in this controversy. In regard to acromegaly, for example, Bailey says that he would not be cited as a defender of the theory that acromegaly is caused by a lesion of the hypothalamus, but thinks that this assumption does not lie outside the bounds of possibility. He believes that the adiposogenital syndrome, when experimentally produced, is caused by injury of the hypothalamic nuclei, but states that this view cannot be definitely accepted until some one succeeds in removing the hypophysis without producing this syndrome and then produces it in the same animal by an experimental lesion of the hypothalamus.

It is also not possible for me to cite in this connection at any length the writings of numerous continental clinicians and experimentalists, but my reading shows me that among them are many men of wide clinical experience who hold that most, if not all, of the clinical states cited above, with the possible exception of Simmonds' hypophyseal cachexia, must not be regarded as being associated with lesions of the hypophysis alone but jointly with lesions of important nerve centers of the hypothalamus and of the hypophysis. In the minds of these writers the neural or hypothalamic nerve center involvement outweighs the endocrine function of the anterior lobe as a causal factor in the explanation of the so-called hypophyseal states.

If I may be permitted to have an opinion of my own in regard to the relationship of the anterior lobe of the hypophysis to the diseased conditions cited above, and to the lesions experimentally induced by surgeons, I would offer a suggestion along the lines made in regard to the posterior lobe. Is it not possible that the pars tuberalis and a portion of the hypothalamus immediately contiguous with the upper part of the hypophyseal stalk possess, if only to a limited extent, the well known growth-promoting hormone of the anterior lobe? My collaborators and I have not yet had the opportunity to test this hypothesis in an experimental way, as was done by us for the posterior lobe hormone. The pars tuberalis was shown by Atwell and Marinus to contain none of the posterior lobe hormone, but it is nevertheless possible that it contains the growth-promoting hormone. If tissue producing this hormone extends even a small way into the hypothalamus, then this fact will perhaps serve to co-ordinate lesions of the hypothalamus and the hypophysis and bring both into harmony with the view that we are dealing in these clinical and experimental conditions rather with a hormone function of the anterior lobe and the upward extending tissue than with lesions of hypothalamic nerve centers, however important these latter may be as neural-regulating mechanisms comparable to others of like nature located elsewhere in the brain.

The experimental zoologists referred to earlier in this lecture have shown that the anterior lobe of the hypophysis, in the case of the amphibia, secretes a hormone which has growth-promoting properties, and that a "replacement" therapy is applicable in these animals in conditions of hypo-function due to lesions of or removal of this lobe. It may be freely admitted that it has not been proved with equal certainty that the anterior lobe plays a similar rôle in mammals. It is, however, my personal view, which I find is shared by others, that it only needs further continued experimentation, coupled with histological and clinical studies, to establish the theory that the anterior lobe secretes a growth-promoting hormone (possessed doubtless of other properties also) on as firm a foundation as has been done for the amphibia. As matters stand, the theory of the endocrine function of the anterior lobe of the hypophysis in the higher animals finds greater support, both in the experimental and clinical knowledge of the day, than does the corresponding theory of the endocrine function of the posterior lobe, but as I have already intimated, I am also optimistic in believing that the ultimate proof of the correctness of the latter hypothesis will soon be forthcoming.

LITERATURE

Abel and Kubota: Jour. Pharm. and Exp. Therap., 1919, XIII, 243.

Abel and Nagayama: Jour. Pharm. and Exp. Therap., 1920, XV, 347.

Abel and Rouiller: Jour. Pharm. and Exp. Therap., 1922, XX, 65.

Abel, Rouiller and Geiling: Jour. Pharm. and Exp. Therap., 1923, XXII, 289.

Abel and Geiling: Jour. Pharm. and Exp. Therap., 1923, XXII, 317.

Addison: Lond. Med. Gaz., 1849, XLIII, 517, and "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules." London, 1855, S. Highley.

Adler: Arch. f. Entwick.mech., 1914, XXXIX, 21.

Allen: Anat. Rec., 1917, XI, 486; Biol. Bull., 1917, XXXII, 117; Science, N. S., 1920, LII, 275.

Aschner: Pflüger's Arch. f. d. ges. Physiol., 1912, CXLVI, 1. Wien. klin. Wchnschr., 1912, XXV, 1042.

Atwell: Science, N. S., 1919, XLIX, 48.

Atwell and Marinus: Amer. Jour. Physiol., 1918-19, XLVII, 76.

Bailey: Erg. d. Physiol., 1922, XX, 162.

Banting, Best, Collip, Campbell and Fletcher: Can. Med. Assn. Jour., N. S., 1922, XII, 141.

Basedow: Wchnschr. f. d. ges. Heilk., Berlin, 1840, VIII, 197, 220.

Bernard: Compt. rend. Acad. d. Sci., Par., 1857, XLIV, 578.

Bert (quoted by Gley): The Practitioner, January, 1915.

Berthold: Arch. f. Anat., Physiol. u. wissensch. Med., 1849, 42.

Biedl: Innere Sekretion, Berlin, 1913.

Bremer: Ann. et Bull. d. l. Soc. roy. d. Sc. méd. et nat. de Bruxelles, 1923, VIII, 129.

Brown-Séquard: Compt. rend. Acad. d. Sc., Par., 1856, XLIII, 422, 542. Arch. de physiol. norm. et path., Par., 1889, 5 s., I, 651, 739.

Burn and Dale: Res. Council London Repts. on Biol. Standards. 1: On the Physiol. Standardization of Ext. Post. Lobe of the Pit. Body, 1922, p. 38.

Camus and Roussy: Titres et Travaux Scientifiques du Dr. J. Camus, 1921, Paris, Imprimerie Chaix.

Carlson and Martin: Amer. Jour. Physiol., 1911, XXIX, 64.

Cowdry: Endocrinology and Metabolism. Appleton, 1922, I, 705.

Cushing: The Pituitary and Its Disorders, Lippincott, 1912.

Cushing and Goetsch: Amer. Jour. Physiol., 1910, XXVII, 60.

Cybulski: Gazeta lekarská, 1895, No. 12; Centralblatt f. Physiol., 1895, IX, 172.

Cyon: Arch. f. d. ges. Physiol., 1898, LXXI, 431; 1898, LXXIII, 339; 1900, LXXXI, 267.

Dale: Biochem. Jour., 1909, IV, 427.

Dixon: J. Physiol., 1923, LVII, 129.

Dixon and Halliburton: J. Physiol., 1916, I, 198.

Dott: Quart. Journ. Exp. Physiol., 1923, XIII, 241.

Dudley: J. Pharm. and Exp. Therap., 1919, XIV, 295.

Engeland and Kutscher: Zeit. f. Biol., 1912, LVII, 527.

Erdheim: Beitr. z. path. Anat. u. z. allg. Path., 1903, XXXIII, 158.

Evans and Long: Anat. Record, 1922, XXIII, 19.

Farini: Gazz. degli Osped., Sept. 11, 1913, cited from Epitome, p. 76, British Med. J., Nov. 29, 1913.

Fontani (quoted by Hyrtl): Lehrbuch d. Anatomie, 1884, p. 878.

Foderà and Pittau: Pathologica, 1909, I, 269.

Frank: Klin. Wchnschr., 1924, III, 847, 895.

Führer: Münch. med. Wchnschr., 1912, 853. Zeit. f. d. ges. exp. Med., 1913, I, 397.

Führer and Pankow: Arch. f. d. ges. Physiol., 1912, CXLVII, 89.

Galen: "Galen on the Natural Faculties," translation by A. J. Brock, 1946, C. P. Putnam's Sons, New York, p. 215; Garrison's History of Medicine, 2nd ed., p. 258.

Gaskell: Quart. Jour. Med. Sci., 1890, XXXI, 379; Jour. Physiol., 1889, X, 153.

Geiling and Kolls: J. Pharm. and Exp. Therap., 1924, XXIII, 1.

Gley: Compt. rend. Soc. biol. Paris, 1891, III, 551; The Practitioner, Jan. 1915.

Graves: London M. and S. Jour., 1835, VII, 516.

Guggenheim: Biochem. Zeit., 1914, LXV, 202.

Gull: Trans. Clin. Soc. London, 1874, VII, 181.

Hadden: Trans. Clin. Soc. London, 1880-1, XIV, 58.

Hanke and Koessler: J. Biol. Chem., 1920, XLIII, 557.

Hédon: Diabète pancréatique, Paris, 1898.

Herring: Quart. Jour. Exp. Physiol., 1908, I, 281; 1914, VIII, 254.

Hogben: Proc. Roy. Soc., 1923, Ser. B, XCIV, 204.

Hogben and Winton: Proc. Roy. Soc., 1922, Ser. B, XCIV, 151; 1923, XCV, 15.

Horsley: Lancet, 1886, I, 3; Brit. Med. Jour., 1906, I, 323; II, 411.

Houssay: La acción fisiológica de los extractos hipofisiarios, 1918, Flaiban, Buenos Aires.

Howell: J. Exp. Med., 1898, III, 215, 245.

Huxley and Hogben: Proc. Roy. Soc., Ser. B, 1922, XCIII, 36.

Hyrtl: Lehrbuch der Anatomie, 17th ed., 1884, p. 892.

Jackson and Mills: J. Lab. and Clin. Med., 1919, V, 1.

Jacobson: Johns Hopkins Hosp. Bull., 1920, XXXI, 185.

Kocher: Verh. d. deutsch. Ges. f. Chir., XII Congress. Arch. f. klin. Chir., 1883, XXIX, 254.

Kolls: J. Pharm. and Exp. Therap., 1920, XV, 443.

Kolls and Geiling: J. Pharm. and Exp. Therap., 1924.

Lépine: Lyon méd., 1889, LXII, 621.

Leschke: Zeit. klin. Med., 1919, LXXXVII, 201; Biochem. Zeit., 1919, XCVI, 50; Verh. f. innere Med., 1922, XXXIV Kongress, 349.

Lewis, Miller and Mathews: Arch. Int. Med., 1911, VII, 785.

Leyko and Sikorski: Medycyny Doświadczalnej i Spolecznej, 1923, I, 1.

Lower: Tractatus de Corde, etc. Cui accessit dissertatio de origine Catarrhi, in qua ostenditur illum non provenire a cerebro, 2nd ed., London, 1670.

Macleod: Brit. Med. Jour., Nov. 4, 1922.

Magnus and Schafer: J. Physiol., 1901-2, XXVII, 9.

Marañon: Bol. soc. españ. de biol., 1911, 120.

Marie: Rev. méd. Paris, 1886, VI, 297.

Mering and Minkowski: Arch. f. exp. Path. u. Pharm., 1889, XXVI, 371.

Minkowski: Berl. klin. Wchnschr., 1887, XXIV, 371.

Moebius: Centralbl. f. Nervenh. u. Psychiat., 1886, IX, 356, 358. Nothnagel's Spec. Path. u. Therapie, 1896, XXII, 1, 202.

Monardes: "Historia medicinal de las cosas que se traën de las Indias occidentales que sirven al uso de Medicina. 1565," translated into German from the Latin translation of Clusius, 1579, by K. Stünzner, 1895, Halle a. S., Verlag von Max Niemeyer.

Mummery and Symes: Brit. Med. Jour., 1908, II, 786.

Murray: Brit. Med. Jour., 1891, II, 796.

Nagayama: J. Pharm. and Exp. Therap., 1920, XV, 401.

Oehme u. Oehme: Deutsch. Arch. f. klin. Med., 1918, CXXVII, 261.

Oliver and Schafer: Jour. Physiol. (Proceedings), 1894, XVI, p. i; 1894-5, XVII, p. ix.

Oliver and Schafer: J. Physiol., 1895, XVIII, 277.

Ord: Med. Chir. Trans. London, 1878, LXI, 57.

Osborne and Vincent: Brit. Med. J., 1900, Mar. 3.

Paulesco: L'hypophyse du cerveau. I. Physiologie, Paris, 1908, Vigot Frères.

Pendé: Endocrinologia, Milano, 2nd ed., 1920.

Reverdin and Reverdin: Rev. méd. de la Suisse romande, Genève, 1883, III, 169, 233, 309.

Robertson: J. Biol. Chem., 1916, XXIV, 397.

Robin (quoted from Gley).

Roca: J. Pharm. and Exp. Therap., 1921, XVIII, 1.

Salvioli and Carraro: Arch. scienz. med., 1907, XXXI, 249; Arch. ital. de biol., 1908, XLIX, 1.

Sandström: abstracted in Hofmann-Schwalbe's Jahresb. ü. d. Fortschritte d. Anat. u. Physiol., 1880, IX, 1.

Schafer and Herring: Proc. Roy. Soc. London, 1906, LXXVII, 571.

Schiff: Untersuchungen über die Zuckerbildung in der Leber, Würzburg, 1859.

Schmidt: J. Lab. and Clin. Med., 1917, II, 711.

Schmidt and May: J. Lab. and Clin. Med., 1917, II, 708.

Smith, M. I., and McClosky: unpublished manuscript.

Smith, P. E.: Anat. Rec., 1917, XI, 57; Univ. Cal. Pub. Physiology, 1918, V, 11.

Strümpel: Deutsche Zeit. f. Nervenh., 1897, XI, 51.

Swingle: J. Exp. Zoology, 1921, XXXIV, 119.

Syz: J. Pharm. and Exp. Therap., 1923, XXI, 263.

Szymonowicz: Arch. f. d. ges. Physiol., 1896, LXIV, 97.

Tilney: Wistar Inst. Memoirs, 1911, No. 2.

Trendelenburg: Berl. klin. Wchnschr., 1924, III, 777.

Uhlenhuth: J. Gen. Physiol., 1920-1, III, 347.

Velden (von den): Berl. klin. Wchnschr., 1913, II, 2083.

Vesalius (quoted by Cushny).

Vincent: The Practitioner, Jan., 1915.

Vulpian: Compt. rend. Acad. sci. Paris, 1856, XLIII, 663. Compt. rend. Soc. biol. Paris, 1859, 2 sér., V, 11.

Weed: Physiol. Reviews, 1922, II, 171.

Weed and Cushing: Amer. Jour. Physiol., 1915, XXXVI, 77.

RHEUMATIC LESIONS OF THE LEFT AURICLE OF THE HEART *

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The pathological anatomy of acute rheumatism has been much discussed recently and the characteristic changes in the heart muscle, pericardium and endocardium well described by Aschoff, Geipel and many others. The object of the present note is to call attention to another distribution of these lesions which, although frequent, has apparently not been observed. The so-called Aschoff bodies are described as occurring most abundantly in the myocardium at the base of the left ventricle and this we have seen also; sometimes indeed they are so large as to be readily visible as whitish flecks to the naked eye. They also occur under the endocardium and something similar is concerned in the lesions upon the valves themselves, although the structure of these vegetations is not indisputably identical with that of the foci in the myocardium.

In a series of cases of rheumatism which we have recently studied, we have found several times a marked thickening of the wall of the left auricle above the base of the more posterior leaflet of the mitral valve. This roughened patch resembles in some degree the vegetations so commonly found there in cases of endocarditis produced by the streptococcus viridans, but is evidently more largely produced by a new growth of tissue and to a less extent by the deposition of rough fibrin on the surface. Sometimes the surface, although corrugated, seems not to be roughened by any thrombus mass. In several cases, the thickened patch appeared to be very dense and scar-like, as though representing the late or healing stage after the subsidence of the earlier process.

Microscopical study shows that in all these cases there are changes in the wall of the auricle and in the tissue about the auriculoventricular junction and the enclosed coronary vessels as well as in the roots of the valves, which resemble those found in the myocardium of the left ventricle but are far more extensive. Most striking is the great oedema and actual new formation of tissue lifting up and spreading apart the inner wall of the auricle inside the muscle. The lining layer of the auricle, very rich in laminated elastic fibrils bound together by intervening fibrillae, is spread apart by fluid and a great infiltration of wandering cells of many sorts. Most of these are mononuclear but there are also many polymorphonuclear leucocytes and there are even lymphatic channels filled with lymphocytes which form a peculiar and rather conspicuous feature. Most striking, however, are the numerous large Aschoff bodies composed of the characteristic large cells with large, deeply staining vesicular nucleus and indefinitely outlined cell body. All the modifications leading to the formation of giant-cell-like masses are seen. These cells are curiously forced into rows by the arrangement of the elastic tissue lamellae so that the Aschoff bodies have a banded appearance. They are numerous and are set along at intervals throughout the whole extent of the patch of thickening. They even extend into the sinus tissue and into the roots of the valves. In most instances the innermost layer of the auricle wall assumes a hyaline appearance over this whole area and merges gradually into a dense film of fibrin which is exposed to the blood of the auricle. Outside the elastic layer where the Aschoff bodies commonly lie, the tissue reaching to the musculature is densely infiltrated with the various wandering cells which in some cases include a number of eosinophiles.

There seems to be no doubt that this is merely a part of the general involvement of the heart wall in the rheumatic process. No new light is shed upon the nature of the Aschoff bodies except, perhaps, that it becomes perfectly clear that the typical large cells are not derived from cardiac muscle.

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THE PROTECTIVE POWER OF NORMAL HUMAN SERUM AGAINST PNEUMOCOCCUS INFECTION*

By Paul W. Clough

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The normal human being undoubtedly possesses a considerable degree of natural immunity to pneumococcus infection. That this resistance is not limited to the relatively avirulent pneumococci belonging to Group IV (and Atypical Type II) which are frequently found in normal mouths, but is also effective against highly virulent organisms of the three fixed types, is suggested by the relatively slight contagiousness of pneumonia of these types, and by the fact that normal individuals may be carriers of these types of pneumococci for considerable periods without developing pneumonia. Very little is really known as to the mechanism of this resistance. Aside from the local mechanical protection which is furnished by the intact mucous membrane of the respiratory passages, it seems possible that there may be antibacterial properties in the blood which also oppose the development of infection.

A study of the blood serum of patients recovering from lobar pneumonia has shown that, in a majority of the cases, the serum has acquired the power of causing agglutination and phagocytosis of the homologous strain or type of pneumococcus, and further has acquired the power of protecting mice from infection with highly virulent strains of the same type. The degree of protective power is slight as compared with that of immune serum, but it may be effective against 10,000 M. L. D. of a culture.[1, 2] The serum of convalescent patients, therefore, possesses in slighter degree those specific activities which are manifested by potent immune serum. It seems probable that the immunity which develops in man on recovery from pneumonia depends in part, at least, upon these acquired properties of the serum, and that the demonstration of the latter may be regarded as an indication of immunity. Of these activities of the serum, protective power is undoubtedly the most significant.

If natural immunity in man depends in part on antibacterial properties of the blood, it seemed possible that a slighter degree of protective power might be demonstrable in the serum of normal individuals, particularly of those normal individuals who possess an unusually high resistance to pneumococcus infection. It has been shown by previous observers, particularly by Neufeld and Haendel,[3] that some specimens of normal serum may protect mice from pneumococcus infection. Cecil and Austin,[4] in connection with their study of the serum of vaccinated individuals, published the results of protection tests with the serum of 16 individuals before vaccination. Of these only one showed any protective power, and this only for a Type I organism. As the smallest dose of culture used by them was 0.0001 c.c., slighter degrees of protective power may have been missed. So far as I know, no other systematic studies of normal serum have been reported.

In the present work I have tested the protective power of the serum of 26 normal individuals against infection with pneumococci of one or more of the fixed types, I, II, and III. With 15 of these sera satisfactory tests were obtained with strains of all three types, while with the eleven remaining sera satisfactory tests were obtained with only one or two of these types.

The technique used was that customary in protection experiments. Cultures of very high virulence were used. 0.0000001 c.c. of an 18-hour broth culture killed the control mice regularly within 48 hours, and 0.00000001 c.c. frequently killed. As determined by plating methods this latter dose contained, on the average, 4 pairs of organisms. The cultures were prepared by inoculating a tube of meat infusion broth (titrated to pH 7.8) with the blood of an infected mouse. Equal volumes (0.2 c.c.) of serum and diluted culture (containing from 0.01 c.c. to 0.0000001 c.c. of culture) were mixed in the syringe and immediately injected intraperitoneally into mice. The mice were observed for 10 days, and in all cases at autopsy the presence of pneumococci in the heart's blood and peritoneum was determined by films or cultures. Unless pneumococci were found in the control mice, the series was rejected. Animals dying after 4 or 5 days and yielding negative cultures were regarded as protected.

A representative protocol is reproduced in Table I.

Of 22 sera tested with a Type I pneumococcus, four had definite protective power (from 10 or more M. L. D. of culture). Of 18 sera tested with a Type II strain, eight had protective power. One serum protected from 1000 M. L. D., and a second serum, in different tests, from 10,000 to 100,000 M. L. D. Of 23 sera tested with a Type III strain, eleven had protective power. Three of these sera protected from 1000 to 10,000 M. L. D.

* Preliminary report read at the annual meeting of the American Society for Clinical Investigation, Atlantic City, N. J., June 14, 1919.

TABLE I.

This experiment was designed to test the protective power of five normal sera against infection in mice with pneumococcus Type II.

No.	Dose of culture (in c.c.)	A Serum None	B Serum M. C.	C Serum H. Gr.	D Serum E. H.	E Serum Fds.	F Serum La.
1.	0.01	....	D. 24 hrs.	D. 39 hrs.	D. 22 hrs.	D. 24 hrs.	D. 20 hrs.
2.	0.001	....	Lived*	D. 23 hrs.	D. 22 hrs.	D. 24 hrs.	D. 20 hrs.
3.	0.0001	....	Lived	D. 45 hrs.	D. 39 hrs.	Lost	D. 72 hrs.
4.	0.00001	D. 18 hrs.	Lived	D. 52 hrs.	D. 39 hrs.	D. 24 hrs.	D. 39 hrs.
5.	0.000001	D. 40 hrs.	Lived*	D. 66 hrs.	D. 52 hrs.	D. 39 hrs.	D. 45 hrs.
6.	0.0000001	D. 41 hrs.	Lived	D. 66 hrs.	D. 18 hrs.	D. 39 hrs.	D. 40 hrs.
7.	0.00000001	D. 52 hrs.	.....	....	....	....	....

* Mice B2 and B5 died after 5 and 7 days, respectively. No organisms were found in films, and cultures were sterile.

In all the other mice which died pneumococci were demonstrated in films or cultures.

The normal serum M. C. protected from 100,000 M. L. D. of culture, while the other four sera tested furnished no protection. This is as great protective power as was found in any normal serum.

The results of these tests with normal serum are given individually in Table II, and summarized in Table III.

If these protection tests with all three fixed types be grouped together, of 63 tests, 23 (or 36.5%) had protective power from 10 M. L. D. or more; 11 (17%) from 100 M. L. D. or more; and 5 (8%) from 1000 to 100,000 M. L. D.

The degree of protective power in the most active sera was therefore as great as that reported by Dochez [1] and by myself [2] in the serum of convalescent patients.

Of the 15 sera tested with all three fixed types of pneumococci, eleven protected from one or more of these types. No one serum, however, protected definitely from all three types. One serum protected from Types I and II; two from Types I and III; and two from Types II and III.

In this series the protective power of the sera against Type I strains was distinctly less than against Types II and III, both in the degree of protection afforded and in the frequency of its occurrence.

Confirmatory tests were carried out with six of the eleven sera which had the most active protective power, and in every case the presence of protective power was again demonstrated. The degree of protective power demonstrated in the confirmatory tests varied somewhat with some of the sera, but in most cases substantially identical results were obtained.

The four sera which had the most active protective power against the Type III pneumococcus strain first used also protected definitely against a second strain of that type.

Twelve sera were also tested for protective power against an Atypical II A strain of moderately high virulence. The results of these tests are also included in the tables. The sera tested with this strain were to some extent selected from those found to be effective against strains of the fixed types, and the percentage of sera that

TABLE II.

Protective power of normal sera tested.

No.	Name	Degree of protection in terms of M. L. D. against infection with pneumococcus of Type: I	II	III	II A	Remarks
1.	P. C.	0	10	10000	0	
2.	M. C.	0	100,000	1000	1000	
3.	E. H.	0	0	100	100	
4.	H. G.	0	10	10	0	
5.	M. H.	0	0	0	100	
6.	Gr.	10	10	1	....	
7.	Bts.	0	1000	0	100	
8.	Pdn.	0	0	0	....	
9.	O. V. W.	0	100	0	1000	
10.	W. C.	0	10	0	10	
11.	P. G.	1	0	0	0	
12.	A. J.	0	0	0	....	Pneumonia twenty-eight years before.
13.	W. M.	0	1000	0	....	
14.	E. B.	10	0	100+	....	
15.	T. C.	100	0	10	....	
16.	C. S.	...	0	1	....	
17.	J. R.	...	0	10	....	
18.	W. K.	0	10	.....	....	
19.	Hk.	0	.....	100	....	
20.	Dty.	10	.....	10	....	
21.	W. Mr.	0	.....	1	....	
22.	D. W.	0	.....	100	....	"Pleural pneumonia" (?) several years previously.
23.	Urn.	...	.....	10	....	
24.	Plr.	...	.....	0	....	
25.	Pn.	0	.....	.....	....	
26.	Ad.	0	.....	.....	....	

TABLE III.

Protective power of normal sera.
Summary of Table II.

Type of pneumococcus	Number of sera tested	Number of sera protecting *	Per cent of sera protecting
I	22	4	18
II	18	8	44
III	23	11	48
Total	63	23	36.5

* From ten or more M. L. D.

protected against it may be higher than would be the case among an average group of normal individuals. While there was often a parallelism between the protective power against Type II and the Atypical II A strain, this was not always the case. A serum might protect definitely against either one of these strains but not against the other. The degree of protective power against the Atypical II A strain, measured in terms of M. L. D., was on the average no greater than that demonstrated against the more virulent organisms of Types II and III, by those sera which protected effectively against these types.

In conjunction with the normal sera, sera from six patients recovering from pneumococcus lobar pneumonia or empyema were also studied. The results are summarized in Table IV. Three of these sera had well marked protective power against an heterologous type of pneumococcus as well as against the type causing the recent infection. I have no data which demonstrate whether this protective power against an heterologous type of pneumococcus developed with recovery from the pneumonia, and was a manifestation of a crossed immunity, or whether it antedated the pneumonia. However, it was probably not a manifestation of a general pneumococcus immunity, since it did not extend to Type III, or (with Serum T. N.) to Atypical II A.

This protective power of normal serum is not due to any direct injury to the organism resulting from their exposure to concentrated serum. Preliminary incubation of the mixtures of protective normal serum and culture did not increase the protective power, but tended to obscure it. This was probably because of multiplication of the organisms at different rates in the various serum mixtures during incubation. Mice were also protected by intraperitoneal injections of serum from intraperitoneal injections of culture two hours later; and by subcutaneous injections of 1 c.c. of serum, from intraperitoneal injections of culture 18 hours later. The protection afforded by subcutaneous injections of serum was somewhat less regular, but was still very well marked. The protocol of such an experiment is given in Table V.

In the tests first carried out, fresh serum only was used. However, the active substances were found to be relatively stable, and during the period of observation very little tendency to deterioration could be demonstrated. One specimen of serum retained its protective power un-

TABLE IV.

The protective power of convalescent human serum against infection with pneumococci of homologous and heterologous types.

No.	Serum	Protective power of serum in M. L. D. against pneumococcus of Type:				Agglutination and phagocytosis of pneumococci of Types:				Previous infection
		Type I	Type II	Type III	Type IIA	Type I	Type II	Type III	Rd.	
1.	T. M.	1000	1000	0	1	++	0	0	—	Type I pneumonia
2.	F. R.	1000	10000	1	100	0	+++			Type II pneumonia
3.	Rd.	100	0	0	100		0		+++	Type IV pneumonia
4.	Fds.	0	0	0	....			+		Type III empyema
5.	Les.	0	0	0	....			+		Type III empyema
6.	Wds.	0	0	100	....			0*		Type III pneumonia two years previously. Type III carrier.

* This serum caused well marked phagocytosis and agglutination of the homologous Type III strain, immediately after recovery from the pneumonia. It was not tested for protective power at that time.

TABLE V.

Experiment to test the effectiveness of various modes of administration of protective normal serum.

No.	Dose of culture (in c.c.)	MODE OF ADMINISTRATION OF SERUM				
		Controls No serum	Subcutan. 18 hours before culture	Intraperit. Two hours before culture	Intraperit. Mixed with culture in syringe and immediately injected	Intraperit. Mixed with culture and incubated one-half hour before injection
1.	0.01	.....	D. 40 hrs.	D. 40 hrs.	D. ? hrs.	D. 40 hrs.
2.	0.001	.....	Lived	Lived	Lived	D. 44 hrs.
3.	0.0001	D. 40 hrs.	D. 44 hrs.	Lived	Lived	Lived
4.	0.00001	D. 40 hrs.	Lived	D. 72 hrs.	Lived	Lived
5.	0.000001	?	Lived	Lived	Lived	Lived
6.	0.0000001	D. 40 hrs.	Lived	Lived	Lived	Lived
7.	0.00000001	Lived	....	....	....	....

The organism used was pneumococcus Type III.

Culture inoculations were all intraperitoneal.

The serum was No. 1, (P. C.), Table II.

This serum protected against 10,000 M. L. D. of culture when culture dilutions and serum were mixed and injected immediately.

Preliminary subcutaneous and intraperitoneal injections of serum afforded marked, but less regular protection.

impaired after inactivation and storage in the ice-box for three months.

A study of the serum failed to reveal any explanation of the mechanism of this protective power. In particular, I was unable to demonstrate agglutinins, bacteriotropins, or precipitins. This is in striking contrast to the usual findings in the serum of patients convalescent from lobar pneumonia.[5]

This contrast is also seen in the behavior of serum T. M., (Table IV), obtained several days after the crisis from a Type I pneumonia. This serum protected mice from 0.0001 c.c. of the stock Type I strain, containing 1000 M. L. D., and caused well marked phagocytosis and agglutination of this strain. It also protected mice to exactly the same extent from a Type II strain, but did not have the slightest agglutinative or phagocytic activity toward that strain. The same behavior is shown by the serum F. R. (Table IV), from a patient recovering from a Type II pneumonia. While this serum protected mice almost equally well from Type I and Type II strains, agglutinative and phagocytic activity was demonstrated only for the Type II strain. If the protective power of immune serum, and of convalescent serum is to be attributed chiefly to these antibodies, as has frequently been claimed, the mechanism of the protective power of these normal sera is apparently different.

The method used for the detection of phagocytic activity in the serum has been described in detail in previous articles.[2,5] A loopful of organisms was rubbed up in a drop of fresh serum, and two parts of this serum suspension were mixed with one part of "leucocytic cream" from a specimen of citrated blood from the individual being tested. The mixtures were incubated without agitation in capillary tubes for periods varying from 30 minutes to 2 hours, and the presence or absence of phagocytosis was determined by inspection of stained films. Only unmistakable degrees of phagocytosis were regarded as significant.

Robertson and Sia [6] have very recently reported a new method of demonstrating pneumococcocidal power of blood (serum and leucocytes). Larger volumes of mixtures are agitated in small sealed tubes during the period of incubation. Destruction of the organisms is shown by failure to recover them by culture or mouse inoculation. They demonstrate that the activity of the leucocytes, presumably phagocytosis, is an essential factor in the process.

It is possible that by the use of a similar method some phagocytic activity could have been demonstrated in the normal sera which exerted protective power. However, even if phagocytic activity be demonstrable by such a method, there would still seem to be a definite disparity between the phagocytic activity of these normal sera, and of convalescent (and immune) sera, as compared with their protective power.

Neufeld and Haendel have supported the suggestion of Dold [7] that the protective power of normal human serum may depend on the slight bactericidal activity it possesses for the pneumococcus, as contrasted with the lack of this activity in the serum of susceptible animals such as the rabbit and mouse. The writer [2] was able to confirm Dold's observations that normal human serum exerts a marked, although temporary, inhibitory effect on the growth of the pneumococcus, if not a slight bactericidal activity, whereas normal rabbit serum does not. However, tests carried out in this laboratory by Dr. Charlotte Van Winkle did not demonstrate any difference in this respect between normal sera which exerted protective power and those which did not. While this capacity of normal serum to inhibit the growth of the pneumococcus may conceivably play some part in the natural immunity of man, it cannot be the explanation of the protective power of the serum.

If the mechanism of the protective power of normal serum be really different from that of immune serum, it seemed possible that by combining immune serum with an actively protective normal serum a summation of their protective power might be achieved. This was tested with a Type III pneumococcus and a specimen of immune serum which was sent from the Rockefeller Hospital by Dr. Rufus Cole, for the routine identification of pneumococcus types. This serum caused marked agglutination and phagocytosis of virulent Type III strains. An injection of 0.2 c.c. of this serum usually protected mice from 0.0001 c.c., of culture (1000 M. L. D.). The normal serum had exactly the same degree of protective power. The combination of 0.2 c.c. of each serum, however, did not protect any better than either one of them alone (Table VI).

TABLE VI.

Experiment to test for summation of protective power of normal serum and immune serum. (Type III.)

No.	Dose of culture (in c.c.)	SERUM USED			
		Controls No serum	Normal: 0.2 c.c.	Immune: 0.2 c.c.	Normal: 0.2 c.c. Immune: 0.2 c.c.
1.	0.5	.....	.....	.....	D. 18 hrs.
2.	0.25	.....	.....	.....	D. 40 hrs.
3.	0.1	.....	D. 18 hrs.	D. 18 hrs.	D. 24 hrs.
4.	0.01	.....	D. 40 hrs.	D. 48 hrs.	D. 40 hrs.
5.	0.001	.....	D. 48 hrs.	D. 48 hrs.	D. 40 hrs.
6.	0.0001	D. 40 hrs.	Lived	D. 90 hrs.	Lived *
7.	0.00001	D. 40 hrs.	Lived	Lived	D. 70 hrs.
8.	0.000001	D. 48 hrs.	Lived	Lived	Lived
9.	0.0000001	D. 48 hrs.	.....	.....	.....

The organism used was pneumococcus Type III.

The normal serum was No. 1, (P. C.), Table II.

The immune serum was a stock diagnostic Type III horse serum.

The combination of the normal serum with the immune serum produced no better protection than did either one alone.

* Mouse died after six days, but no organisms were demonstrated in films, and cultures were sterile.

The question might be raised as to the possibility of the therapeutic use of such sera, particularly in case of Type II and Type III pneumonia. It seems most improbable that it could be of any practical value, both because of the relatively feeble activity of the sera, and of the difficulty in finding suitable donors. Neither would it probably be effective in supplementing the activity of an immune serum.

Conclusions as to the significance of this protective power of normal sera must be drawn with the greatest reserve until further data have been accumulated. That it was not the result of recovery from a previous recognizable lobar pneumonia could be excluded with certainty by the history in most of the cases. None of the subjects had received pneumococcus vaccine. Neither was it necessarily associated with the existence of a carrier state at the time of the test. Several of the individuals whose serum was most highly protective were examined with reference to this point. Only one carrier of a fixed type organism was found, a Type III. This man (Wds., Table IV) was not classed as normal, and was included in the series because he was known to be a carrier. He had had a Type III pneumonia two years previously. His serum in two different tests protected mice from 100 M. L. D. of the homologous Type III strain. In two patients who had recovered from Type III empyema, however, the serum did not have the slightest protective power against the homologous strains. It would be interesting to determine the frequency of protective power in the serum of such carriers of fixed type organisms.

While direct evidence is lacking, it seems probable, as suggested by Cecil and Blake,[8] that repeated exposure to pneumococcus infections, which is inevitable under present living conditions for a large part of our population, results in building up "a fair degree of immunity against the microorganism." The protective power of the serum might be an indication of such an immunity.

It seems a reasonable assumption that the presence of protective power in a normal serum would indicate the possession by the individual of a weapon of defense against infection, and would be presumptive evidence of some degree of natural immunity. This assumption is strengthened by the studies of Cecil and Austin[4] on the serum of individuals who had received polyvalent pneumococcus vaccine. They found that the serum in most cases exerted definite protective power for mice against Type I and Type II strains, and less frequently against Type III also. The effectiveness of the vaccination was shown by the relatively lower incidence of pneumonia among the vaccinated, as compared with the unvaccinated. The degree of protective power they found was about the same as that of the most active normal sera I have examined.

However, Cecil and Blake[9] in their experimental work with monkeys did not find an exact parallelism between the protective power or demonstrable antibody content of the serum and the resistance of the animals to intratracheal injections of culture. Some animals whose serum had protective power, developed pneumonia on inoculation, while some animals proved to be immune, notwithstanding the absence of protective power in their serum.

While the protective power of the serum cannot be regarded as an accurate quantitative index of the immunity of an individual, it may still be considered the most reliable indirect evidence now obtainable of the existence of an immunity. Undoubtedly local conditions in the lung and respiratory passages play an important part and possibly the most important part in determining the development of pneumonia. It seems probable, however, that the presence of protective power in the serum of normal individuals, as well as of vaccinated individuals, will usually indicate a relatively high degree of resistance to infection.

Summary

The protective power for mice of the serum of normal individuals was tested against infection with highly virulent strains of pneumococci of the three fixed types. Definite protective power (from 10 or more M. L. D. of culture) was demonstrated in 4 of 22 sera tested against pneumococcus Type I; in 8 of 18 sera tested against pneumococcus Type II; and in 11 of 23 sera tested against pneumococcus Type III.

The degree of protective power was usually slight, but in five instances, the serum protected from 1000 to 100,000 M. L. D. This is as high a degree of protective power as has ordinarily been found in the serum of vaccinated individuals, or of patients recovering from acute lobar pneumonia.

Protective power against one type of pneumococcus was not necessarily associated with protective power against other types. Of 15 sera tested against all three fixed types, none protected definitely against all three; five sera protected against two of the three types; and eleven against one or more of the three types. Sera which protected against Type II pneumococci usually but not invariably protected also against an Atypical II A strain, and vice versa.

None of the normal individuals studied had received pneumococcus vaccine. One only had a history of a long antecedent pneumonia. None of those most actively protecting were found to be carriers of a fixed type pneumococcus.

The serum of the only carrier of a fixed type pneumococcus available for study (two years after recovery from a Type III pneumonia) had protective power against that type.

The normal sera that protected most effectively against a fixed type pneumococcus caused no agglutination or phagocytosis *in vitro* of that type, in contrast with the

sera of convalescent patients, which (like immune sera) usually possessed marked agglutinative and phagocytic activity, as well as protective power for the type of organism causing the recent infection. No difference was found between the slight bactericidal power of normal sera which exerted protective power and of those which did not protect. No explanation of the mechanism of the protective action of normal serum was found, but it apparently differs in some details at least from that of immune serum.

The combination of a highly protective normal serum with immune serum did not protect any better against Type III infection than did either one alone.

Further observations will be required to determine the significance of this protective power. It seems probable that it is a manifestation of one of the important defensive mechanisms in natural immunity.

The not infrequent spontaneous occurrence of protective power in the serum must be kept in mind in the study of vaccinated, or otherwise artificially immunized, individuals.

REFERENCES

1. Dochez, A. R.: The presence of protective substances in human serum during lobar pneumonia. J. Exper. Med., Lancaster, Pa., 1912, XVI, 665-679.

2. Clough, P. W.: The development of antibodies in the serum of patients recovering from acute lobar pneumonia. Bull. Johns Hopkins Hosp., Baltimore, 1913, XXIV, 295-306.

3. Neufeld, F., and Haendel: Ueber die Entstehung der Krisis bei der Pneumonie, und über die Wirkung des Pneumokokkenimmunserums. Arb. a. d. k. Gsndhtsamte., Berl., 1910, XXXIV, 166-181.

4. Cecil, R. L., and Austin, J. H.: Results of prophylactic inoculation against pneumococcus in 12,519 men. J. Exper. Med., Baltimore, 1918, XXVIII, 19-41.

5. Clough, P. W.: Phagocytosis and agglutination in the serum in acute lobar pneumonia; the specificity of these reactions and the regularity of their occurrence. Bull. Johns Hopkins Hosp., Baltimore, 1919, XXX, 167-176.

6. Robertson, O. H., and Sia, R. H.: Studies on pneumococcus growth inhibition. II. A method for demonstrating the growth-inhibitory and bactericidal action of normal serum-leucocyte mixtures. J. Exper. Med., Baltimore, 1924, XXXIX, 219-244.

7. Dold, H.: Die bakterizide Wirkung des Blutes, Plasmas, und Serums auf Pneumokokken, und ihre Bedeutung für die Immunität. Arb. a. d. k. Gsndhtsamte., Berl., 1911, XXXVI, 419-432.

8. Cecil, R. L., and Blake, F. G.: Studies on experimental pneumonia. IV. Results of prophylactic vaccination against pneumococcus pneumonia in monkeys. J. Exper. Med., Baltimore, 1920, XXXI, 519-553.

9. Cecil, R. L.: Discussion: American Soc. Clin. Investigation: Jour. Am. Med. Assn., Chicago, 1919, 73: 785.

THE TREATMENT OF POST-ENCEPHALITIC PARKINSON SYNDROME WITH HYOSCIN HYDROBROMIDE, WITH A NOTE ON THE MENTAL ATTITUDE IN THIS SYNDROME AND A REPORT OF 18 CASES

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Erb [1] in 1901 recommended hyoscin hydrobromide in 2-4 decimilligram doses, once or twice a day, as a very important palliative measure to relieve the tremor, rigidity and limb restlessness (Gliederunruhe) in paralysis agitans. In his experience the drug could be given over long periods of time (years) without loss of efficacy or any need for increasing the dosage except perhaps slightly. Furthermore, there were practically no uncomfortable or serious complications from its use.

In July, 1921, Babinski [2] and Souques [3] reported the use of hyoscin in the post-encephalitic Parkinsonian syndrome. They regarded it as the best palliative remedy of the many drugs tried. They used both hypodermatic and oral administration. Striking improvement was noted in some of their cases, although they found the drug without effect in others. The only untoward symptoms observed as a result of the medication was the temporary appearance of somnolence, vertigo, and ocular symptoms (loss of accommodation and blurring of vision). These all disappeared promptly with the reduction or discontinuance of the drug. Kennedy, Davis, and Hyslop [4] reported briefly on its use. In November, 1922, Hyslop [5] published his results in the treatment of eight patients and compared the value of hyoscin with that of gelsemium and other drugs (adrenalin, nicotine, picrotoxin, pilocarpin and morphin). Hyslop found beneficial results in six out of the eight patients treated. His conclusion is that it "reduced tremor and rigidity, restored mobility of the facies, and enabled patients to walk and use the arms more freely."

Our own observations were made solely with hyoscin hydrobromide and we are reporting 18 cases so treated. These 18 have been gathered from the patients admitted to the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, the out-patient department of the Phipps Clinic, and from my own practice. These were all cases of the

Parkinsonian syndrome following epidemic encephalitis; only those have been included in which we felt that the results were decisive.

Our first patient was treated in April 1921, and the improvement noted was so striking that since that time we have treated all similar cases with doses of hyoscin hydrobromide sufficiently large to obtain optimal results. The maximum amount has been 1/50 gr. four times a day. The average dose has been about 1/100 gr. four times a day. In not a single instance has it been necessary to increase the dosage because of any acquired tolerance for the drug. No bad effects have been observed, and the patients have experienced no uncomfortable symptoms except some difficulty in accommodation, vertigo and somnolence, while the dosage was being regulated. As soon as the effective therapeutic dose was determined, this accommodation difficulty and other untoward symptoms disappeared. One exception should be noted. In Case 9, 1/150 gr. four times a day was insufficient to keep the patient relaxed; 1/100 four times a day made him stuporous. He was, however, an uncooperative patient and I suspect that he did not take the medication as directed.

In every one of the 18 cases, objective improvement has been noted. The mental attitude of the patients is an important item with which to deal. I have observed that the "rigidity" is not confined to the body musculature, but that the personality also assumes an analogous rigidity. The emotional responses of the patients are limited, ambition is at low ebb;—their energy does not seem sufficient to make them use their available physical energy; and they are usually reduced to a dull, complaining monotony. After the initial amelioration of symptoms, the patients become insensible to the really great improvement that has occurred. A drastic but helpful demonstration to them is to take them off the drug completely, and they immediately become aware of the great difference. The need for encouragement is great and the patients have also to be treated in much the same way as any chronic invalid with a very incapacitating disease. In addition, one finds the mental rigidity and monotonous complaining which seem to me due to an essential personality change due to the disease.

I have reported the 18 cases in tabular form and have graded the improvement as slight, definite, or marked. Of the 18 patients, six were slightly improved, five definitely improved, and seven markedly improved. I have regarded as indicative of marked improvement the following results: Return to work after months of invalidism, and ability to attend to personal wants after being bedridden and helpless. Under definite improvement, I have included those patients who have returned to full activity after partial invalidism. Slight improvement indicates some relaxation of the rigidity, but not enough to increase the practical efficiency of the individual. The improvement in mental attitude has been very striking in a number of patients. It is important to recognize the essentially organic etiology of the mental rigidity and to realize that this class of patients should not be grouped as psychoneurotic.

We have tried hyoscin in other epidemic encephalitic residuals, psychoneurotic-like states, depression and overtalkative states, and in the behavior disturbances in children and adults. In none of these cases have we noted any improvement. I should like to emphasize again, as I did in a former communication,[6] that the psychoneurotic states, although most advantageously treated as psychogenic, are probably due to organic changes.

Our cases seem to me to emphasize again the need for a carefully guarded prognosis after the original acute attack, because of the late onset of the Parkinson sequelae. In our series, the average time elapsing between the onset of Parkinson symptoms and the original acute attack was 16 months. In one patient, this interval was as long as five years.

Conclusions

1. Hyoscin is a very valuable palliative remedy in post-encephalitic Parkinson syndrome.

2. Hyoscin hydrobromide may be prescribed in doses as high as 1/50 gr. four times a day.

3. The change in mental attitude (mental and emotional rigidity) should be understood to form a part of the disease.

REFERENCES

1. Erb, W.: Paralysis Agitans (Parkinson'sche Krankheit). Deutsche Klinik., 1901, VI, Abt. I, 31-50.

Erb, W.: Gessamelte Abhandlungen, 1864-1910. 2 Bde. Leipz., 1910, F. C. W. Vogel.

2. Babinski, J.: Les syndromes parkinsoniens. Réunion Ann. de la Soc. de Neurol. de Par. (Discussion); Presse méd., 1921, XXIX, 524-527.

3. Souques, A.: Les syndromes parkinsoniens. Presse méd., 1921, XXIX, 524-527.

4. Kennedy, F., Davis, T. K., and Hyslop, G. H.: An additional contribution to the symptomatology of epidemic encephalitis. Arch. Neurol. & Psychiat., 1922, VIII, 40-46.

5. Hyslop, G. H.: The treatment of residual epidemic encephalitis. J. Neurol. & Psychopath., 1922-23, III, 250-261.

6. Hohman, L. B.: Epidemic Encephalitis (Lethargic Encephalitis). Its Psychotic Manifestations, With a Report of Twenty-three Cases. Arch. Neurol. & Psychiat., 1921, VI, 295-333.

Patient	Age	Sex	Occupation	Date first seen	Date of acute attack of epidemic encephalitis	Date onset Parkinsonian syndrome	Symptoms	Medication (Hyoscin hydrobromide), in grains	Results General	Specific: Motor	Specific: Mental	Comment
(1) (2966) F. K.	20	M.	Clerk	4/16/21	Jan. 1920	Fall 1920	General rigidity; tremor of left hand; forced movements in right leg. Periodic dyspnea and dysphagia; propulsion gait. Bedridden. Hopeless.	1/100 t. i. d. and at 8 P. M.	Definite improvement.	Some relaxation of rigidity. Diminution of tremor. Able to feed himself. Able to walk a little.	More cheerful and interested. Exaggeratedly hopeful.	Would now use larger doses.
(2) O. W. (3078)	33	M.	Machinist	7/21/21	Sept. 1920	Sept. to Dec. 1920	General rigidity; hand tremors; gait unsteady. Reversal of sleep curve. Development of violent temper and brutality. Suicidal.	1/150 t. i. d.	Slight improvement.	Some relaxation of rigidity. Diminution of tremor.	Slight improvement.	
(3) W. M. C. (3222)	38	M.	Farmer	10/ 4/21	Jan. 1919	Jan. 1919	Profound rigidity (bedridden). Marked salivation. Complete psychobiologic inactivity.	1/150 t. i. d. and at 8 P. M.	Slight improvement.	Slight relaxation of rigidity. Decrease in salivation. Able to walk length of ward.	A little increase in energy. Was able to write home.	
(4) J. M. (3317)	31	M.	Merchant	11/29/21	Nov. 1919	Jan. 1921	General rigidity. Right hemiparesis with tremor. Discouraged. Sleepless. Lack of ambition and hope.	1/100 b. i. d.	Definite improvement.	Relaxation of rigidity and tremor. Able to feed himself. Tries dancing.	Much more hopeful. Attempting simple work. Improvement in sleep.	
(5) R. D. (3347)	20	M.	Clerk	7/10/22	Feb. 1920	Mar. 1920	General Parkinsonian rigidity with propulsion and retropulsion; constant tremor of left side of body. Intention tremor of both sides. Dysarthria. Practically bedridden.	1/150 t. i. d. and at 8 P. M.	Definite improvement.	Able to walk. Attempted to dance. Fed himself. Washed himself. Improved speech.	More alert and interested.	Would now try larger doses.
(6) V. H. B. (3441)	23	M.	Student	11/ 2/22	Apr. 1920	Nov. 1920	General rigidity, propulsion gait. Tremor of arms and legs.	1/100 t. i. d. and at 8 P. M.	Slight improvement.	Tremor decreased. Less propulsion.	Some decrease in discouragement.	Would now try larger doses.
(7) C. P.	29	M.		1/—/23	May 1920	Jan. 1922	General profound rigidity with salivation. Had to be fed, washed, and attended "like an infant."	1/50 t. i. d. and at 8 P. M.	Marked improvement. Return to simple work. Can take care of self completely.	+++ Relaxation of rigidity. Disappearance of salivation.	Hopeful, much more action. More energy.	
(8) A. W.	24	F.	Housewife	10/22/23	1921 No febrile attack	Spring 1923	General rigidity. Asthenia. Inactivity. General fatigue tremor. Depression. "Ocular spasms."	1/75 t. i. d. and at 8 P. M.	Definite improvement. Able to do more work in less time.	+ Relaxation of rigidity. Diminution of "ocular spasms." Absence of tremor. Loss of asthenia.	More energetic. Loss of depression. General speeding up of psychobiologic reactions.	
(9) W. R.	23	M.	Taxi-driver	11/—/23	No febrile attack	Fall 1922	General rigidity. "Dopy feeling." "Ocular spasms." Slowness of movement. Automatic flexion of legs. Arm in position of flexion.	1/150 t. i. d. and at 8 P. M.	Marked improvement.	Relaxation of rigidity and automatic leg flexion.	Disappearance of "dopy" feeling.	Patient so much improved that he regarded himself as well and discontinued medication. Had to return again.

Patient	Age	Sex	Occupation	Date first seen	Date of acute attack of epidemic encephalitis	Date onset Parkinsonian syndrome	Symptoms	Medication (Hyoscin hydrobromide), in grains	Results General	SPECIFIC		Comment
										Motor	Mental	
(10) M.H.B. (3765)	35	M.	Salesman	11/21/23	1919	Summer 1922	General rigidity. General slowing. Coarse tremor of hands—more on left. Left arm in position of flexion (position of election). Smacking tic of lips. Staccato speech. Depression. Unable to work.	1/100 t. i. d. and at 8 P. M.	Marked improvement.	Relaxation of rigidity. Increase in speed of reactions. Diminution of tremor. Decrease of lip tic.	More active. Disappearance of depression. Return to work.	
(11) H. S. (3785)	31	M.	Civil Engineer	12/22/23	Mar. 1920	Mar. 1920	General rigidity. Tremor of left arm. Intention tremor of both arms. Depression and anxiety. Hypochondriasis.	1/150 t. i. d.	Slight improvement.	Decrease in rigidity and tremor.	No change in mental condition.	
(12) K. S.	14	M.	Student	9/29/20	Feb. 1920	Apr. 1920	Rigidity. Sleep curve reversal; spitting; "behavior disturbance."	1/100 t. i. d. and at 8 P. M.	Slight improvement.	Relaxation of rigidity.	Subjective increase in energy.	
(13) F. B.	29	F.	Housewife	1/15/24	1919	Fall 1923	General rigidity. Weakness. Crying spells. General psychobiologic slowing.	1/100 t. i. d. and at 8 P. M.	Marked improvement. Return to full work.	+ + Relaxation of rigidity. Cessation of crying spells. Cessation of weakness.	More energetic and hopeful.	
(14) F. D.	26	M.	Potter	1/15/24	1918	Summer 1923	General rigidity. Flexor attitude of hands. Inactive, somnolent. Stammering. Psychobiologic rigidity.	1/100 t. i. d. and at 8 P. M.	Marked improvement.	+ + Relaxation of rigidity. Relaxation of flexor attitude of arms. Abolition of stammering.	More cheerful, hopeful and ambitious.	
(15) A. R.	43	F.	Housewife	2/12/24	1921	Apr. 1923 (?)	General rigidity. Asthenia. Tremor of hands, lack of ambition. Vague general hypochondriasis. Stammering.	1/75-1/50 t. i. d. and at 8 P. M.	Definite improvement.	Decrease in rigidity and tremor. Less weak.	More energetic. Still very hypochondriacal.	
(16) O. O.	18	M.	Student	4/ 2/24	Feb. 1, 1923	Summer 1923	General rigidity. Asthenia. Tremor of hands. Lack of ambition. Vague general hypochondriasis. Stammering.	1/100 t. i. d. and at 8 P. M.	Marked improvement with return to work.	+ + Relaxation of rigidity with increased activity. Cessation of tremor.	More cheerful, hopeful.	
(17) J. J.	43	M.	Factory Foreman	4/12/22	1919	1920	Profound rigidity and salivation. Nervous, inactive, lacking in ambition.	1/50 t. i. d. and at 8 P. M.	Very slight improvement.	+ Relaxation of rigidity; abolition of salivation.	No increase in ambition or energy.	
(18) E. L. W.	28	M.	Lawyer	12/11/22	1919 (?)	June (?) 1922	Restlessness; irritable; depressed; difficulty in concentration. Lack of ambition. Parkinsonian rigidity. Right arm in flexion as position of election. Tremor of right arm.	1/150 t. i. d.	Marked improvement.	Relaxation of rigidity. Disappearance of tremor. Flexion position absent.	Hopeful; disappearance of depression; return of ambition.	

BOOKS RECEIVED

Pediatrics. By various authors. Edited by Isaac A. Abt, M. D. Volume III. With 223 illustrations. 1924, 8°. 1051 pages. W. B. Saunders Company, Philadelphia and London. $10.00 per volume.

American College of Surgeons. Eleventh year book. 1924, 8°. 633 pages. Chicago.

The Surgical Clinics of North America. Mayo Clinic number. Volume 4, No. 2, April, 1924, 8°. 598 pages. W. B. Saunders Company, Philadelphia and London Cloth, $16.00 per year; paper, $12.00.

The Parathyroid Glands in Relation to Disease. By H. W. C. Vines, M. A., M. D. 1924, 8°. 128 pages. Edward Arnold & Co., London. $3.50.

The Surgery of the Peripheral Nerve Injuries of Warfare. Being the Hunterian Lectures delivered before the Royal College of Surgeons of England on February 7th and 9th, 1921. By Harry Platt, M. S., Lond., F. R. C. S. Eng., 1921, 8°. 49 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

The Prevention of Dental Caries and Sepsis. By H. P. Pickerill, C. B. E., M. D. Third edition. 1924, 8°. 340 pages. Paul B. Hoeber, New York. $6.00.

Maternity Nursing in a Nutshell. By Elizabeth H. Wickham, R. N. With 28 illustrations. 1924, 8°. 167 pages. F. A. Davis Company, Philadelphia. $1.50.

The Relative Position of Rest of the Eyes and the Prolonged Occlusion Test. By F. W. Marlow, M. D., M. R. C. S. Eng., F. A. C. S. Illustrated with original diagrams and charts. 1924, 8°. 96 pages. F. A. Davis Company, Philadelphia. $2.50.

Cosmetic Surgery. The Correction of Featural Imperfections. By Charles Conrad Miller, M. D. With one hundred and forty illustrations. 1924, 8°. 263 pages. F. A. Davis Company, Philadelphia. $4.00.

Differential Diagnosis. Presented through an analysis of 317 cases. By Richard C. Cabot, M. D. Third edition, revised, profusely illustrated. Vol. 11, 1924, 8°. 709 pages. W. B. Saunders Company, Philadelphia and London. $9.00.

Diseases of Middle Life. The Prevention, Recognition and Treatment of the Morbid Processes of Special Significance in this Critical Life Period. Comprising twenty-two original articles by various eminent authorities. Edited by Frank A. Craig, M. D. In two volumes. Illustrated. 1923, 8°. 951 pages; 920 pages. F. A. Davis Company, Philadelphia. $15.00.

Management of Diabetes. Treatment by Dietary Regulation and the Use of Insulin. A manual for Physicians and Nurses based on the Course of Instruction given at the Presbyterian Hospital, New York. By George A. Harrop, Jr., M. D. Introduction by Walter W. Palmer, M. D. 1924, 8°. 176 pages. Paul B. Hoeber, New York. $2.00.

Fifty Years of Medical Progress 1873-1922. By H. Drinkwater, M. D., Edin., M. R. C. S. Eng., F. R. S. E. With thirty-seven illustrations on thirty-five plates. 1924, 12°. 183 pages. The Macmillan Company, New York. $4.00.

A Study of Masturbation and Its Reputed Sequelae. By John F. W. Meagher, M. D., F. A. C. P. 1924, 8°. 69 pages. William Wood and Company, New York. $1.50.

Excursions into Surgical Subjects. By John B. Deaver, M. D., Sc. D., LL. D., F. A. C. S., and Stanley P. Reimann, M. D. Illustrated. 1923, 8°. 188 pages. W. B. Saunders Company, Philadelphia and London. $4.50.

Diphtheria. Its Bacteriology, Pathology and Immunology. By Frederick W. Andrewes, William Bulloch, S. R. Douglas [and others]. Medical Research Council. 1923, 8°. 544 pages. Published by His Majesty's Stationery Office, London. $4.50.

New York Hospital. Collected Papers from the Second Surgical Division. Surgical Staff, Eugene H. Pool, M. D., F. W. Bancroft, M. D., P. A. Dineen, M. D., Steward Erdman, M. D., J. A. Vietor, M. D., E. M. Hawks, M. D., Alma Vedin, M. D. 8°.

Epitome on Blood Pressure. Aids to the Interpretation of Blood Pressures for the General Practitioner with Key to Diagnosis. By Burton Baker Grover, M. D. 1924, 16°. 78 pages. The Electron Press, Kansas City. $3.00.

Psycho-Analysts Analysed. By P. McBride, M. D., F. R. C. P. E., F. R. S. E. With introduction by Sir H. Bryan Donkin, M. D. (Oxon.), F. R. C. P. 1924, 12°. 142 pages. William Heinemann, London. 3/6 net.

Insulin in General Practice. A Concise Clinical Guide for Practitioners. By A. Clarke Begg, O. B. E., M. D., Ch. B. (Edin.), M. B. (Lond.). With four diagrams. 1924, 12°. 130 pages. William Heinemann, London. 5/– net.

The Human Testis. Its Gross Anatomy, Histology, Physiology, Pathology, with Particular Reference to its Endocrinology, Aberrations of Function and Correlation to other Endocrines, as well as the Treatment of Diseases of the Testes and Studies in Testicular Transplantation and the Effects of the Testicular Secretions on the Organism. By Max Thorek, M. D. 308 illustrations. 1924, 8°. 548 pages. J. B. Lippincott Company, Philadelphia and London. $8.00.

Papers from the Mayo Foundation for Medical Education and Research and the Medical School. 11, 1921-22. 1923, 8°. 716 pages. W. B. Saunders Company, Philadelphia and London. $13.00.

Rockefeller Institute for Medical Research, Studies. Reprints. Volume XLVIII. 1924, 8°. 597 pages. New York.

Diabetes. A Handbook for Physicians and their Patients. By Philip Horowitz, M. D. With thirty-four text illustrations and two colored plates. Second edition, revised and enlarged. 1924, 8°. 219 pages. Paul B. Hoeber, New York. $2.00.

Bulletin of the International Association of Medical Museums and Journal of Technical Methods. Managing editors. Maude E. Abbott, M. D. and Major James F. Coupal. No. X. 1924, 8°. 165 pages. Paul B. Hoeber, New York. $3.00.

American Proctologic Society, Transactions. Twenty-fourth annual session, 1923. 1924, 8°. 89 pages. Paul B. Hoeber, New York. $3.00.

Common Symptoms of an Unsound Mind. A Guide for General Practitioners. By G. Rutherford Jeffrey, M. D., F. R. C. P. E., F. R. S. E. With a foreword by Sir James Crichton Browne, M. D., LL.D., D. Sc., F. R. S., F. R. S. E. 1923, 12°. 268 pages. Paul B. Hoeber, New York. $2.50.

College of Physicians of Philadelphia. Transactions. Third series, volume forty-five. 1923, 8°. 856 pages. Philadelphia.

The Medical Clinics of North America. McGill University Number. Vol. 7, No. 6, May, 1924, 8°. W. B. Saunders Company, Philadelphia and London. $12.00 per year.

Human Physiology. A Practical Course. By C. G. Douglas, C. M. G., M. C., D. M., F. R. S. and J. G. Priestley, M. C., D. M. 1924, 8°. 232 pages. Oxford University Press, American Branch, New York; Clarendon Press, Oxford.

Operative Surgery. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By Warren Stone Bickham, M. D. and Phar. M. (Tulane)—M. D. (Columbia)—F. A. C. S. Containing 6378 illustrations, many in colors. Volume IV, 1924, 8°. 842 pages. W. B. Saunders Company, Philadelphia and London. $10.00 per volume.

Fasting and Undernutrition. A Biological and Sociological Study of Inanition. By Sergius Morgulis. 1923, 8°. 407 pages. E. P. Dutton & Company, New York. $5.00.

The Leucocyte in Health and Disease. Being an Enquiry into Certain Phases of Leucocytic Activity. By C. J. Bond, C. M. G., F. R. C. S. With forty-eight illustrations in twenty-four plates. 1924, 8°. 84 pages. H. K. Lewis & Co., Ltd., London.

Anesthesis. By James Tayloe Gwathmey, M. D. With collaborators on special subjects. Illustrated. Second revised edition. 1924, 8°. 799 pages. The Macmillan Company, New York and London. $6.50.

Modern Methods of Treatment. By Logan Clendening, M. D. With chapters on special subjects by H. C. Andersson, M. D.; J. B. Cowherd, M. D.; Carl O. Rickter, M. G.; F. C. Neff, M. D.; E. H. Skinner, M. D., and E. R. DeWeese, M. D. Illustrated. 1924, 8°. 692 pages. The C. V. Mosby Company, St. Louis. $9.00.

Life Insurance Examination. Edited by Frank W. Foxworthy, Ph. B., M. D. One hundred and fifty-six illustrations. 1924, 8°. 738 pages. The C. V. Mosby Company, St. Louis. $9.00.

The Internal Secretions. By Arthur Weil. Authorized translation of the third German edition. By Jacob Gutman, M. D., Phar. D., F. A. C. P. 1924, 8°. 287 pages. Macmillan Company, New York.

A Manual of Practical X-Ray Work. By John Muir, B. Sc.; M. B.; Ch. B.; B. Sc. (Pub. Health). In collaboration with Sir Archibald Reid, K. B. E., C. M. G., M. R. C. S., L. R. C. P., D.M.R.E. (Camb.) and F. J. Harlow, B.Sc., F. Inst. P., A. B. C. Sc. Being a third edition of the manual by Arthur & Muir. 1924, 8°. 524 pages. Paul B. Hoeber, New York. $10.00.

Clinical Aspects of the Electrocardiogram. A Manual for Physicians and Students. By Harold E. B. Pardee, M.D. With fifty-six illustrations. 1924, 8°. 222 pages. Paul B. Hoeber, New York. $4.00.

A Dictionary of Treatment. Including Medical and Surgical Therapeutics. By Sir William Whitla, M.D., D.Sc., LL.D. M.P. Seventh edition. 1924, 8°. 1100 pages. Paul B. Hoeber, New York. $10.00.

A Diabetic Manual for the Mutual Use of Doctor and Patient. By Elliott P. Joslin, M.D. Third edition, thoroughly revised. Illustrated. 1924, 16°. 211 pages. Lea & Febiger, Philadelphia and New York. $2.00.

The Evolution of Man. Essays. By G. Elliot Smith, M. A., M. D., Litt. D., D.Sc., F.R.C.P., F.R.S. 1924, 8°. 159 pages. Oxford University Press, American Branch, New York.

Goiter: Nonsurgical Types and Treatment. By Israel Bram, M. D. 1924, 8°. 479 pages. Macmillan Company, New York. $6.50.

The Cure of Pulmonary Tuberculosis by Rest and Exercise. By Hugh M. Kinghorn, M.D. With illustrations from photographs. [1924.] 8°. 169 pages. Richard G. Badger, The Gorham Press, Boston. $2.50.

A Medical Guide to the Principal British Spas and Climatic Health Resorts. By the Editor of the Health Section of the Medical Directory, with the Assistance of the Medical Officer of Health and Medical Committees in the Localities. 1924-5, 8°. 90 pages. J. & A. Churchill, London. One shilling net.

Mind and Medicine. By Thomas W. Salmon, M.D. 1924, 8°. 33 pages. Columbia University Press, New York.

The Primitive Archaic Forms of Inner Experiences and Thought in Schizophrenia. By Dr. Alfred Storch. Nervous and Mental Disease Monograph Series No. 36. 1924, 8°. 111 pages. Nervous and Mental Disease Publishing Company, New York and Washington. $2.00.

Baltimore Health Department. Department of Public Safety. Annual report Sub-Department of Health. To the Mayor and City Council of Baltimore for the Fiscal Year ended December 31, 1923. 1924, 8°. 276 pages. Baltimore.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. with the collaboration of Chas. H. Mayo, M.D. Volume II. Thirty-fourth series. 1924, 8°. 306 pages. J. B. Lippincott Company, Philadelphia and London. $2.00.

Dysentery in the Federated Malay States. By William Fletcher, M.D. Camb. and Margaret W. Jepps, with a preface by Dr. A. E. Horn, C. M. G. Studies from the Institute for Medical Research, Kuala Lumpur, Federated Malay States. No. 19. 1924, 8°. 82 pages. John Bale, Sons & Danielsson, London.

Die Eklampsie. Von Paul Bergell, Max De Crinis, Gerhard Denecke, [*et al.*] Herausgegeben von Hans Hinselmann. Mit 13 Tafeln und 52 Abbildungen im Text. 1924, 8°. 952 pages. Friedrich Cohen in Bonn. $9.45.

The Circulatory Disturbances of the Extremities. Including Gangrene, Vasomotor and Trophic Disorders. By Leo Buerger, M. A., M.D. With 192 illustrations, five in colors. 1924, 8°. 628 pages. W. B. Saunders Company, Philadelphia and London.

Cancer. How it is Caused; How it can be Prevented. By J. Ellis Barker. With an introduction by Sir W. Arbuthnot Lane, Bart., C.B., M.S., F.R.C.S. 1924, 8°. 478 pages. E. P. Dutton & Company, New York. $3.00.

Diabetes; Its Treatment by Insulin and Diet. A Handbook for the Patient. By Orlando H. Petty, B.S., A.M., M.D., F.A.C.P. With several illustrations. 1924, 12° 111 pages. F. A. Davis Company, Philadelphia. $1.50.

An Introduction to the Study of the Mind. For the use of medical students, beginners in psychiatry, social workers, and all those interested in mental hygiene. By William A. White. Nervous and Mental Disease Monograph Series No. 38. 1924, 8°. 116 pages. Nervous and Mental Disease Publishing Co., Washington, D. C.

The Medical Department of the United States Army in the World War. Volume XI, Surgery. Part two. Prepared under the direction of Maj. Gen. M. W. Ireland, M. D. 1924, 4°. 827 pages. Government Printing Office, Washington, D. C.

A Memoir of William & John Hunter. By George C. Peachey. 1924, 8°. 313 pages. Printed for the author by William Brendon and Son, Plymouth, England.

Manual of the Diseases of the Eye. For Students and General Practitioners. By Charles H. May, M.D. Eleventh edition, revised. With 374 original illustrations including 23 plates, with 73 colored figures. 1924, 12°. 445 pages. William Wood and Company, New York. 1924. $4.00.

The Carbohydrates and the Glucosides. By E. Frankland Armstrong, D. Sc., Ph.D., F.R.S., F.I.C. Fourth edition. 1924, 8°. 293 pages. Longmans, Green and Company, London. $5.00.

NOTES ON NEW BOOKS

Quain's Elements of Anatomy, Vol. IV, Part II: *Myology* by E. H. BRYCE, *Sections on the Actions of Muscles* by THOMAS WALMSLEY, 11th Edition. $8.00. *(New York, Longmans, Green and Co., 1923.)*

The time has passed when the musculature of the human body may be studied on a purely descriptive basis. In a modern text-book of human myology we expect the field to be attacked from several angles. First, the description must be based on embryology and comparative anatomy, as has been done in a masterly way in the older text-book of C. Gegenbaur. Second, the field must be dealt with from the standpoint of function as is done in more recent text-books. Furthermore, we expect an adequate appreciation of the facts important in practical medicine. The recently (1921) edited text-book of Human Anatomy by H. Braus, Vol. I, really unites all these demands. Braus' unexcelled book is therefore an ideal text-book for instructors and for the best of our students. However, it is too extensive to become generally used by students.

The present volume (IV) of Quain's Human Anatomy does not come up to the high standard of Braus' excellent text-book. The fact, however, that the field is viewed from a standpoint of comparative morphology and function makes the book valuable.

The volume is divided into two portions: first, a short section on general myology, followed by the main part on descriptive myology. At the end of the book is found a list of important contributions to the literature, arranged according to subjects—a very valuable addition. Though not intended to be in any sense exhaustive, this list will form a good guide for the student to penetrate into the enormous literature which exists on this field.

In the first part on general myology a few pages are devoted to a consideration of general muscle mechanics. The next chapter deals with the morphology of the skeletal musculature. It is pointed out that the very complex human musculature can be understood properly only from the standpoint of embryology and comparative anatomy, since the knowledge of the developmental history of muscles organizes the great mass of descriptive material and brings scientific order into the subject. Of special interest is the attempt which is made to correlate the muscles of arm and leg, of hand and foot, and to trace them back to an ideal ground-plan, typical for tetrapodal vertebrates. A more thorough understanding of these principles would certainly make the study of the extremities a fascinating one. To many students the study of the musculature and innervation of the extremities is a tedious task, and is therefore rather neglected, so that many a student's knowledge of gross human anatomy ends with the trunk and the extremity-plexuses.

The succeeding very short chapter on Variations of the Musculature is valuable. It is pointed out that the muscular system is extraordinarily variable, and that a large number of variations can only be understood on a basis of comparative anatomy. Hence the genetic relationship of man to other mammals and especially to the group of Primates is briefly discussed. It would have been very helpful if a few instructive examples of the innumerable would have been given in illustration of these facts. One is disappointed not to find included in this chapter references to the racial differences in musculature; however, a few of the more important works on this subject have been incorporated in the bibliography at the end of the book. There exists already a large literature on this field. In the future, considerations of Racial Anatomy will certainly play an important rôle, especially in text-books used in many American dissecting-rooms where Negroes and Whites are dissected side by side.

The second part on descriptive myology is mainly written in the routine style of an ordinary text-book, comparative anatomical considerations having been added now and then. A large part of the text is given to a description of the fasciae and the tendon sheaths of the muscles of the extremities. A short description with clear illustrations and emphasis on the practical value of these structures would have been preferable.

On the other hand, the short résumés on Innervation of Muscle Groups, given at the end of the different chapters are valuable. Of greatest importance are the concise discussions of the action of the muscle groups. In teaching in the dissecting-room much more stress should be laid on analyzing the complex actions, in which generally a whole muscle group is involved, than on considering separately the probable function of the single muscles which have been dissected out.

The second section of the book is begun by the description of the Cutaneous Muscles of the Head. The amazing investigation of facial musculature gives, much better than the study of any other muscle group of the human body, a clear understanding of how, through gradual differentiation from a simple ground-plan, the whole muscle group has developed. Not less than forty facial muscles have separated off from two primitive muscle layers, the Platysma and Sphincter colli profundus. This differentiation has taken place within the group of mammals and has in Prosimiae and Primates reached a very high specialization, to form the very complex mimetic musculature of higher apes and man. Thus a comparative study of the facial musculature in Prosimiae and Primates, as has been laid down in its principles by the famous work of G. Ruge, supplies the basis for a thorough understanding of the human facial musculature. Such a comparative anatomical study of greatest value from both the didactic and scientific standpoints would lead the student to an understanding of the innumerable variations which occur in the human facial musculature. Well marked racial differences, as has been stated in a number of papers, would make the consideration of this muscle group still more interesting, and a chapter on facial expression would complete the study.

The author, however, discusses very briefly only the embryological development of the facial muscle group, based on the results of R. Futamura's very doubtful studies. Then he continues with an uninteresting account of the different single facial muscles, as it is done in ordinary text-books. A short paragraph on the action of the muscles of the scalp and face ends this chapter.

After the description of the Muscles of Mastication, the author devotes a chapter to the Muscles of the Orbit. One might rather expect to find a consideration of these muscles in connection with the eye in the volume on the sense organs, the more since the author has not included the intrinsic ear muscles in this volume.

In the chapter on the Muscles of the Neck the writer has accepted a number of erroneous statements on innervation of muscles scattered through the literature. They are contrary to a clear understanding of the ontogenetical and phylogenetical development of muscles, since they lead to the belief that the study of the nerve-supply is not an infallible guide to the morphology of a muscle. I would like to mention, for example, statements on page 69 regarding the innervation of M. sterno-cleido-mastoideus through the hypoglossal nerve and

through twigs of the superior laryngeal; on page 70 regarding the discussion of the assumed secondary innervation of sterno-cleido-mastoideus and trapezius through spinal nerves; and on page 73 the statement that the innervation of the anterior belly of Digastricus through twigs of the N. mylo-hyoideus is a secondary one.

In the chapter on the Musculature of the Tongue a simple diagram of the N. XII and the arcus and ansa hypoglossi could have made clear the often discussed fact that the tongue muscles are innervated through pure fibers of N. XII whereas the supra- and infra-hyoid muscle-groups receive branches from the cervical plexus (C 1-3). Instead, it is stated erroneously, on page 72, that the M. thyreo-hyoideus is innervated from the trunk of the hypoglossal.

In the chapter on the Back Musculature the author deals only with the intrinsic back musculature, having described the more superficial back muscles in connection with the muscles of the neck and upper limb, i. e., with the rib musculature (Serratus posticus sup. and inf.). The dissection and study of the intrinsic back muscles is generally disliked by students as well as by instructors. This is not justifiable, since this muscle group is bound to become highly important for the orthopedic surgeon. Eugen Mathias in Zürich has shown that orthopedic gymnastics based on a thorough understanding of the vertebral column and the intrinsic back musculature lead to very good results in correcting curvatures of the spine. This practical side should be emphasized in teaching in the dissecting room. The study of the very complex human back musculature could be made simpler and more interesting by considering this muscle group more from a functional and a comparative anatomical point of view, in correlation with the normal and pathological curvatures of the vertebral column, and in connection with the acquisition of the upright posture in man. For a study of this muscle group clear figures, showing the dissection of the different layers in their extension over the whole back would be one of the first requirements. Instead of this only three, rather poor, uninstructive figures are added to the text.

Following the description of the Muscles of the Thorax and Diaphragm an interesting discussion is inserted regarding the function of the respiratory muscles.

The chapter on the Abdominal Muscles is followed by a detailed account of the Perineal Muscles and the pelvic and perineal fasciae.

In the chapters on the Muscles of the Extremities additional figures of the skeleton indicating muscle attachments would certainly have been very valuable for the understanding of the detailed description of origin and insertion of these muscles. The recapitulating short discussions on innervation are very useful. Thus, the student, after having dissected and studied the simple muscles, is enabled to consider them together in their phylogenetical groups. The description of the distribution and the course of the nerve branches will be helpful to the student during the dissection; on the other hand, it may form a valuable guide to the orthopedic surgeon. The paragraphs on function are of greatest value in this chapter. The types of movements possible in the different joints are discussed in a clear manner, and then the complex movements, in which generally a number of muscles take a share, are analyzed. Thus these paragraphs on function are stimulating to both students and instructors.

In brief, I conclude that the present volume on the muscular system of Quain's Human Anatomy contains in its short first section stimulating chapters on the general principles of function and on the morphological basis for the study of the field. The second descriptive section is written mainly in the routine style of text-books. However, the paragraphs on innervation of the phylogenetical muscle groups, and especially the short clear paragraphs on function, make the book valuable.

The B. N. A. terminology is generally employed, thus making the use of the book in different countries easier.

The illustrations to the text are mediocre, some of them rather poor.

On the whole, this textbook can be recommended to students and teachers. E. H.

An Introduction to the Practice of Preventive Medicine. By J. G. Fitzgerald. 1922, 8°, 826 p. $7.50. *(C. V. Mosby Co., St. Louis.)*

With the advent of new books on public health and preventive medicine, one hopes for something which will bring out a new point of view. It is with a certain regret, therefore, that one finds in the present volume the usual conventional treatment of the subject. The book is, however, well done and presents the collected facts of preventive medicine in a clear and useful manner. The comments on Canadian methods are especially illuminating from the point of view of American readers who may well take a leaf from the book of their neighbors across the border. A. L. B.

How We Resist Disease. An Introduction to Immunity. By Jean Broadhurst, Ph. D. 138 illustrations and 4 color plates. 1923, 8°, 248 p. $2.50. *(J. B. Lippincott Co., Phila. and London.)*

It is not easy to deal with the subject of Immunity in a practical way for nurses or for students in elementary biology. The subject, even as treated in this book, is certainly too complex and too detailed to find a place in the curriculum of the nurses' training school. On the other hand, the book falls short of being a good reference work. At best it can only be regarded as suitable for supplementary reading on the part of those who are so inclined. The general plan of the book is good. Many of the illustrations and charts are well chosen. However, it is feared that something of accuracy is sacrificed in the effort for simplicity. It seems unfortunate, even for nurses, that the Wassermann reaction should be chosen as a typical illustration of the complement fixation reaction "with syphilitic organisms as antigen." The discussion of the employment of lysins for forensic diagnosis of blood stains is very misleading. There are errors in the legends of some of the illustrations. The author is fond of the use of diagrammatic illustrations. It seems to the reviewer that this is overdone. Such diagrams tend to commit the inexperienced reader to one theory or another and the theory is likely to obscure the phenomenon—certainly an unfortunate attitude of mind for nurses. A good deal of liberty has been taken in modifying the diagrams of other authors. The chapter on Vaccines is particularly good, and that on Anaphylaxis is also good. J. H. B.

A Textbook of Chemistry for Nurses. By Fredus N. Peters, A. M., Ph. D. 2d Edition. 1923, 8°, 302 p. $2.50. *(C. V. Mosby Co., St Louis.)*

This little work is very complete and would make an excellent textbook for nurses' classes. It is written in a simple, interesting and easy reading style. It gives the necessary information without being too technical. L. C.

Practical Chemical Analysis of Blood. By VICTOR C. MYERS, M. A., Ph. D. 2d Edition. 1924, 8°, 232 p. $4.50. *(C. V. Mosby Co., St. Louis.)*

The new edition of this excellent manual brings it up to date both from the standpoint of the methods and also from that of interpretation of the analytical data given. The selection of the methods and the clearness and accuracy of their presentation leave nothing to be desired. The clinical laboratory worker will find in this book a valuable and dependable guide not only for the details of practical analytic technic but also for a sane interpretation of his results. The discussion of the literature is presented by the author in a masterly fashion and should greatly help the clinician to orient himself in the mass of chemical data which is rapidly accumulating in regard to various pathologic conditions. Some of the more important problems, such as retention of nitrogenous constituents, carbohydrate tolerance and acidosis are discussed particularly well and exhaustively. In the opinion of the reviewer this book is the best manual of blood analysis available at present. W. A. P.

The parathyroid glands in relation to disease. By H. W. C. VINES, M. A., M. D. 1924, 8°, 128 p. $3.50. *(Edward Arnold & Co., London.)*

This monograph seems to have been written primarily to sing the praises of dessicated parathyroid substance. Rheumatoid arthritis, varicose ulcers, epilepsy, Parkinson's Disease, chorea, and still some more, are all asserted to be cured or benefited by treatment with this product. Parathyroid tetany, which ought to be benefited if dessicated parathyroid substance has any therapeutic virtues, is not included in the long list of conditions improved or cured. It is difficult to understand why the author adopted as a test of activity the ability of parathyroid substance to destroy guanidine *in vitro* when a more convincing test would have been the demonstration of its capacity to raise the level of calcium in the serum of the parathyroidectomized animals. There is good reason to doubt the existence of any relationship between parathyroid tetany and guanidine intoxication.

The author has briefly summarized our knowledge of the gross and microscopical anatomy of the parathyroid glands and has discussed their relationship to the other endocrine organs and to calcium and carbohydrate metabolism. Emphasis is laid upon the importance of the parathyroids in all conditions in which the calcium metabolism is disturbed.

We venture to predict that this monograph will be quoted widely by the manufacturers of "endocrine products," as furnishing additional "scientific proof" of their contentions. B. K.

An Introduction to the Study of Mental Disorders. By FRANCIS M. BARNES, JR., M. A., M. D. 2d Edition. 1923, 8°, 295 p. $3.75. *(C. V. Mosby Co., St Louis.)*

The present volume combines the introduction to the study of mental diseases and the notes on mental diseases which the author used in his teaching in the St. Louis University Medical School. It is a formal statement, both in the general and in the special part. The present day dynamic conceptions find very little space in the book. A. M.

Fighting Foes Too Small to See. By JOSEPH MCFARLAND, M. D., Sc. D. 1924, 8°, 309 p. with 64 illustrations. $2.50. *(F. A. Davis Co., Phila.)*

We have in this book by Dr. McFarland, Professor of Pathology in the Medical Department of the University of Pennsylvania, what has been long needed—the popular yet accurate presentation of the romantic story of microbiology. The historical references, the literary quotations and the choice of illustrations are particularly pleasing, although some of the sixty-four illustrations are poorly reproduced. The book should be read not only by the general public, but also by medical men who will find it full of profitable interest. W. L. H.

Methods in Medicine. The Manual of the Medical Service of George Dock, M. D., Sc. D. By GEORGE R. HERMANN, M. D., Ph. D. $6.50. *(St. Louis, C. V. Mosby Co., 1924.)*

It has been found useful in the Robert A. Barnes Hospital, St. Louis, to formulate or rather to develop a set of rules for the House Officer. The published manual is meant to be a "practical ward or bedside guide." It contains full directions for the student clinical clerks, and after outlining routine methods of hospital administration for a total of about 110 pages goes on to Part II which in 105 pages gives clinical laboratory directions and which seems to be quite complete for the moment. Part III consists of 100 pages about diets. Part IV is devoted to therapeutic methods, including emergency measures, as well as a brief discussion of the uses of "Dock's Twenty Drugs." Part V shows charts and request forms which have very little interest to any but the Barnes Hospital staff.

Organizers of medical services will find parts of this book very interesting. House Officers will appreciate it as a quick reference in medical emergency and as an easy approach to clinical laboratory instructions, but it does not appeal to the reviewer as a book of wide usefulness. H. M. T., Jr.

Fifty Years of Medical Progress, 1873-1922. By H. DRINKWATER, M. D. 183 pp., $4.00. *(New York, The Macmillan Co., 1924.)*

In his preface, the author says "Without doubt, the last fifty years must be looked upon as the golden age of medical progress, not only because of the immense number of new facts discovered, but also because of their practical application." The half century dealt with is from 1873 to 1922 inclusive. He points out that in the former year Lister was still experimenting with the carbolic spray in the wards of the Royal Infirmary at Edinburgh. Antiseptic surgery was in its infancy, to be followed later by surgical asepsis. The great boon to humanity, directly referable to the pioneer work on the cause of fermentation and suppuration by Lister and Pasteur, falls largely within this period. A new science has arisen—Bacteriology—the term for which had not been introduced in 1873.

The events leading up to the discovery of the etiology of tuberculosis, plague, diphtheria, leprosy, cholera, gonorrhoea, syphilis, malaria, yellow fever, hydrophobia, typhoid fever, are duly recorded. New diseases, such as Vincent's angina, Weil's disease, Barlow's disease and trypanosomiasis, were first described during this period and the essential data given. No reference is made to encephalitis lethargica, which came into prominence after the pandemic of influenza of 1918 to 1919. The development of our knowledge concerning immunology, the endocrine glands, vitamins, and the roentgen rays, is epitomized.

The arrangement of the material in this volume of 183 pages is very convenient for purposes of reference. The diseases, the organs and the therapy have been arranged alphabetically. Under each heading, the dates of the chief events connected with the subject are placed chronologically. There are many photographs of the men who have contributed to the lustre of this "golden age" of medicine.

Medical writers, physicians and students will find a wealth of information in readily available form in this little volume. There is a useful index both of subjects and authors. T. B. F.

Introduction to Medical Biometry and Statistics. By RAYMOND PEARL. $5.00. *(W. B. Saunders Co., Philadelphia and London, 1923.)*

Almost every medical man has to resort to the use of statistics at some time or other. He may need to know the incidence of a certain disease or of a certain complication of a disease; or he may need to know quantitatively the percentage of cures to be expected following a certain operation, or following the use of a certain drug. If he is content to rely upon superficial impressions in analyzing data he will almost habitually misinterpret results, especially group results, both in his own work and in reading accounts of that of others.

While an acquaintance with statistical methods would doubtless do much to prevent physicians from misinterpreting statistics, it is obvious that acquiring this information by reading would be quite a difficult task for any one who does not possess a mathematical viewpoint.

While this book has been written from experience in teaching statistics to physicians and other students of public health, its function is rather that of a textbook than that of a reading book. For the former purpose, its merits are certainly beyond question.

Too much commendation cannot be placed upon the excellent manner in which Dr. Pearl has presented a very difficult subject. Scarcely a page can be read without giving an impression of fineness, unquestionable soundness and logic. The chapter on medical records is particularly commendable and, being relatively free from technical material, lends itself well to reading by medical men. A set of 17 diagrams at the end of Chapter VI is another part of the book that should interest and aid the non-technical reader. V. L. E.

The Antiquity of Disease. By ROY L. MOODIE. 1923, 12°, 148 pp. $1.50. *(University of Chicago Press, Chicago.)*

This small book is devoted especially to the evidences of disease processes which have been found in the fossilized skeletons of pre-historic animals. It is said to be written "not only for the specialist but also for the educated layman." Although it impresses one as being rather technical for the layman and somewhat vague for the specialist, it is, nevertheless, an entertaining summary of the problems and possibilities of the science of paleopathology.

Of course, the obvious limitations of the subject material do not permit this work to compare in interest with such delightful and daring studies as those of Marc Armand Ruffer on the gross and histological pathology of ancient Egyptian mummies; for here one has to be content with fossilized skeletal structures, losing completely all traces of the diseases which may have ravaged the viscera and soft parts. However, fossil pathological specimens are by no means dull and unromantic objects. They make up in awesomeness of age much of what they lack in fleshiness. In comparison with these stark fragments of strange, long past times when the very face of the earth was different from that of today, the mummies of Merneptah and Amenhotep enter our thoughts with the intimate warmth and friendliness of contemporaries.

The study of the lesions in fossil bones is undoubtedly very important work. It is, for example, a matter of considerable interest from the standpoint of the evolution of pathological reactions to know that the oldest fracture yet discovered, which dates from the darkness of the Permian period, had healed apparently in much the same manner in which fractures heal today. But the most careful study and the most expert pathological and paleontological opinion are required before one can feel safe in the interpretation of most of the various fossil lesions encountered. One is left with the impression that many of the bone changes described represent necroses and exostoses of very uncertain nature and origin. Wherever the nature of the process appears to be clear, one will always be much more impressed by the fact that such reactions to injury were in operation thousands of years ago, than by the most nimble attempt of the paleopathologist to guess just what the inciting injury may have been. Indeed, the dignity of the narrative is occasionally compromised by enthusiastic theorizing and by attempts to reconstruct from a fragment of bone the life and manners of the creature of which it formed a part some eons ago. An illustration of how imaginative and interpretative a paleopathologist can be on occasion may be found in the following quotation. Discussing certain necroses of obscure origin found in the bony carapaces of the Pleistocene glyptodonts, the author writes: "Dr. Sinclair, of Princeton, suggests that these necrotic sinuses were caused by injuries from the sabre-toothed cat which in attacking the glyptodont, and finding himself baffled by the bony armor, clawed and bit the carapace of the beast. If the giant Pleistocene cat's teeth and claws were as septic as the modern house cat's are reputed to be, sepsis may well have followed such an attack." But such passages were probably written for the educated layman rather than for the specialist. A. R. R.

A CORRECTION

In a letter dated September 11, 1924, Dr. Hugh H. Young writes as follows:

In the June issue of the *Bulletin*, 1924, (XXXV, 165), I presented the following article: "Preliminary Report of a Case of Mixed Sex, an Apparent Male, with a Testis in Scrotum on Right Side; Ovary, Tube and Uterus in Inguinal Canal on left side." In this paper I stated that in my opinion this was the first human case of true glandular hermaphroditism recorded. I now find that this was an error, in that a paper entitled, "True Bilateral Hermaphroditism with Periodic Hematuria" had been presented for publication in the Journal of Urology on November 18, 1923. It now gives me great pleasure to correct this error and to call attention to this other remarkable case.

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